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THE TREATMENT OF PYURIA DUE TO BACILLUS COLI*

A. HECHT JOHANSEN, M.D.
Assistant Physician, Bispebjaerg Hospital, Copenhagen
BOSTON

It is well known that a culture of *Bacillus coli* will become sterile on standing at 37 C., as the colon bacilli are killed by the acid that they themselves produce. Test-tube experiments have shown that the acid culture fluid has a growth-inhibiting, or a deadly, effect on colon bacilli. Thus, a number of authors (Winslow and Lochridge, 1906,[1] Michaelis and Marcora, 1912,[2] Clark, 1915,[3] Dernby, 1921,[4] and Warburg and I, 1925,[5]) have demonstrated that the growth of *B. coli* is inhibited with a hydrogen ion concentration of about p_H 5.

In 1921, Haldane [6] showed that the urine may be acidified to a degree corresponding to about p_H 5 by the oral administration of calcium chloride and ammonium chloride; and in 1924-1925, Warburg and I used this method on patients with infections of the urinary tract as a therapeutic measure against these lesions. In some cases this treatment was augmented by the additional administration of methenamine, as this substance proved particularly effective in acid fluid. The results, published in *Acta medica Scandinavica*,[5] showed recovery in about 50 per cent of the cases. At about the same time, Beckmann and van der Reis [7] obtained concordant results with a similar therapy.

As it was evident from these investigations that the disinfecting action of methenamine in infections of the urinary tract is dependent on the acidity of the urine, I thought that it would also be of interest to find out whether some similar condition applies to phenyl salicylate, which has been used for a great many years as a urinary disinfectant.

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* From Medical Department B, Bispebjaerg Hospital, Copenhagen. Physician in chief: E. Meulengracht.

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As is well known, phenyl salicylate is a compound of salicylic acid and phenol that passes through the stomach without undergoing any change; in the intestines it is split into its components, both of which are rapidly absorbed and leave the organism by way of the urine, as phenol —the disinfecting part of phenyl salicylate—is combined with sulphuric acid and glycuronic acid.

While the urine is still in the bladder, fermentative processes may cause a splitting of this last compound, whereby phenols are set free once more; and it is the oxidation of these phenols that gives the urine its eventual "phenyl salicylate-coloring".

As a rule, phenyl salicylate is given in doses of from 2 to 5 Gm. daily, usually together with some acid potion—for instance, Mixtura acidi sulfurici,[8] which contains 0.25 per cent sulphuric acid. If the idea here is to acidify the urine in order to further the effect of phenyl salicylate, the usual 3 or 4 tablespoonfuls of the "acid mixture" in twenty-four hours is too small a dose, as Warburg and I have mentioned;[5] for 3 times 15 cc. of "acid mixture" contains about 20 cc. of tenth-normal mineral acid, while 3 times 1 Gm. of calcium chloride corresponds to 75 cc. of tenth-normal mineral acid.

The use of phenyl salicylate is usually discontinued when the urine becomes phenyl salicylate-colored, for fear of toxic effects from the phenol. The clinicians who have used phenyl salicylate have noticed that, all other factors being equal, some patients show phenyl salicylate-colored urine more rapidly and more readily than do others for no demonstrable reason and, what is more important, without any indication of increase in disinfecting effect concurrent with the phenyl salicylate color.

In spite of the phenyl salicylate-colored urine, however, administration of phenyl salicylate has been continued for weeks without causing the patient to give any sign of toxic phenomena.

Briefly, such are the guiding principles of phenyl salicylate therapy.

My aim in this investigation has been the attempt at forming some idea—partly from my own experiments, partly on the basis of clinical observations—as to the extent to which the disinfecting effect of phenyl salicylate against *B. coli* is dependent on the reaction of the urine.

I have not taken up the chemic-analytic aspect of the problem, with its qualitative and quantitative determination of the split products that may be formed in the urine and eventually be active in the various phases of the phenyl salicylate treatment. On the other hand, I have tried to

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8. ℞

	Cc.
Acidi sulfurici dilute	20
Syrupi rubi idaei	180
Aqua destillatae	800
	1,000

find out whether it is practicable during phenyl salicylate treatment to demonstrate any differences in the disinfecting action of the urine against *B. coli* on different experimental conditions.

TECHNIC

Briefly, the technic is as follows:

Sterile urine is obtained from a patient whose urinary tract is healthy. The specimen is divided into four or five portions, to which hydrochloric acid and sodium hydroxide are added in such amounts as to give a series of differing specimens with p_H ranging, for instance, from 6.6 to 4.8, with suitable intervals.

I have chosen the zone from p_H 6.6 to 4.8, as it is within this interval that one may alter p_H of the urine by means of medicamentation—with calcium chloride, for instance.

Under sterile precautions, equal amounts (5 cc., for instance) are pipetted from the various portions of urine of different hydrogen ion concentration (for instance, with p_H 6.4, 5.7, 5.3 and 5) into sterile test tubes. In addition, one should have on hand a number of tubes containing sterile broth.

TABLE 1.—*Data Obtained in a Series of Transplants (No Medicamentation)* *

	First Inoculation, Urine	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H		Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
7.0	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
6.2	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.2	+ +	— —	+ +	— —	+ +	— —	+ +	— —	+ +
4.5	— —	— —	+ +	— —	+ +	— —	+ +	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
7.0	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..
6.2	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..
5.2	.. ..	.. ..	.. ..	+ +	.. ..	+ +	.. ..	+ +	.. ..
4.5	.. ..	.. ..	.. ..	+ +	.. ..	— —	.. ..	— —	.. ..

* In this table and in tables 2, 3, 4, 5, 6, 7, 8, 9 and 10, + indicates visible growth; (+) indicates a considerable inhibition of growth, and —, no visible growth.

Now, transplants are made from a culture of an actively growing, pathogenic strain of *B. coli* into two tubes of each kind of specimen of urine of different acidity, and the tubes are left in the incubator for four hours; then transplants are made from each of these tubes into tubes containing urine of the same p_H as well as into tubes containing ordinary broth. All these transplants are placed in the incubator, and four hours later, new transplants are made from the last ones in the same manner, etc.

The data obtained in such a series of transplants are given in table 1. The results of the transplantations are read after twenty-four hours. From all tubes not showing visible growth, fresh transplants are made into tubes containing broth in order to find out whether the lack of visible growth is due to inhibition of growth or to killing of the bacilli.

The transplants were made every four hours to imitate, as far as possible, the conditions in the organism, when one assumes the bladder to empty itself every four hours. These four hours then leave time for the bacilli to grow as well as time for the eventual bactericidal substances in the urine to counteract the bacterial growth.

I then gave phenyl salicylate, 1 Gm. four times daily, to the same patient for four days and repeated the previously described culture experiments with the same colon strain on portions of the same sterile urine, differing in degree of acidity, and with the same transplants, the same time intervals, etc., as in the foregoing experiment. The results of these experiments are given in table 2.

A third series of experiments was carried out with the same patient. This the same oblique line—from the bottom at the left and upward to the right—just as it does in table 1; consequently, the more acid the urine, the fewer transplants are required for sterility.

A third series of experiments were carried out with the same patient. This time he was given calcium chloride for several days, until the urine gave an acid reaction to methyl red; this reaction was kept up, while the patient received phenyl salicylate, 1 Gm. four times daily for four days. The same experiments

TABLE 2.—*Data Obtained in a Series of Transplants After the Administration of Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.2	+ +	+ +	+ +	+ +	+ +	+ +	+ +	— —	+ +
5.7	+ +	— —	+ +	— —	+ +	— —	+ +	— —	+ +
5.3	+(+)	— —	+ +	— —	+ +	— —	+ +	— —	+ +
5.0	— —	— —	+(+)	— —	(+)(+)	— —	(+)(+)	— —	(+)(+)
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.2	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	.. ..	+ +	.. ..
5.7	.. ..	+ +	.. ..	+ +	.. ..	+ +	.. ..	— —	.. ..
5.3	+ +	+ +	.. ..	— —	.. ..	— —	.. ..	— —	.. ..
5.0	+ —	— —	.. ..	— —	.. ..	— —	.. ..	— —	.. ..

TABLE 3.—*Data Obtained in a Series of Transplants After the Administration of Calcium Chloride and Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.3	+ +	— —	+ +	— —	+ +	— —	— —	— —	— —
5.7	— —	— —	+ +	— —	+ +	— —	— —	— —	— —
5.3	— —	— —	+ +	— —	— —	— —	— —	— —	— —
4.9	— —	— —	+ +	— —	— —	— —	— —	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.3	+ +	(+)(+)	.. ..	+ +	.. ..	— —	.. ..	— —	.. ..
5.7	+ —	— —	.. ..	— —	.. ..	— —	.. ..	— —	.. ..
5.3	— —	— —	.. ..	— —	.. ..	— —	.. ..	— —	.. ..
4.9	— —	— —	.. ..	— —	.. ..	— —	.. ..	— —	.. ..

as before were repeated in an analogous manner. The results are given in table 3.

This table shows the same acclivity for the transition from + to — growth; but, as will be noticed, the line has shifted definitely upward to the left, which indicates that the urine has a more disinfecting effect in the last experiment.

This fact is still more obvious when the points at which sterility is ascertained are marked on a coordinate system with the p_H values along the abscissa and the number of transplants along the ordinate. The outcome will be two curves of different courses: one curve for the experiment in which the patient was given phenyl salicylate alone, and a different curve for the experiment in which the patient's urine is acidified, previous to the ingestion of phenyl salicylate, by means of calcium chloride (chart 1). The greater disinfectant power of the urine in the last case is manifest in the smaller number of transplants as well as in its germicidal action in spite of the higher p_H values.

I have repeated these experiments in the same manner with two more patients with healthy urinary tracts and with two other pathogenic strains of *B. coli*; the results obtained were similar to those of the experimental series just mentioned, although to a less pronounced degree. They are given in tables 4, 5 and 6 with the corresponding chart 2, and in tables 7, 8 and 9 with the corresponding chart 3. In charts 2 and 3, the degrees of acidity and the numbers of transplants

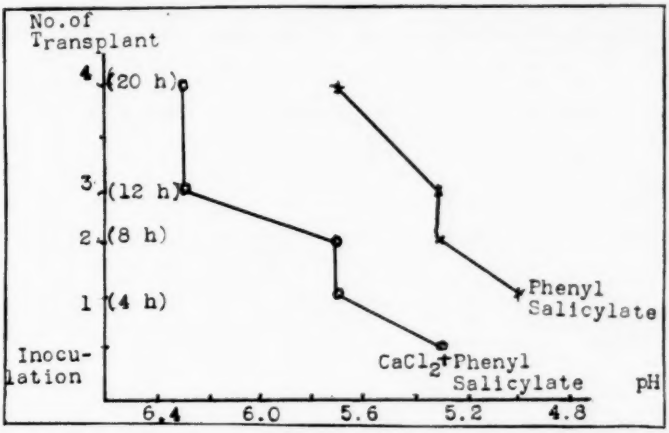

Chart 1.—Curves representing the results in tables 2 and 3.

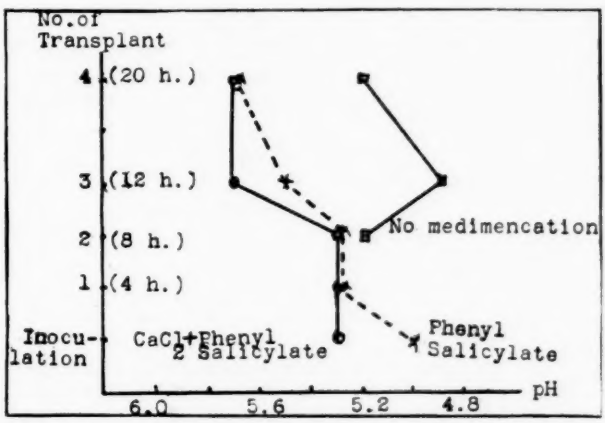

Chart 2.—Curves representing the results in tables 4, 5 and 6.

at which sterility first appeared are recorded in the same manner as was done in chart 1.

Obviously, the colon strains that are used in the last two series of experiments show a lesser degree of difference in sensitivity when the experiments are made, respectively, with ordinary urine, with urine containing phenyl salicylate and with urine that is kept acid during the phenyl salicylate treatment. I cannot say

whether one might be able to make the difference more conspicuous by carrying out the experiments with a series of urines of differing acidities, in which the difference in p_H is smaller than that in these experiments.

TABLE 4.—*Data Obtained in a Series of Transplants (No Medicamentation)*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.4	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.6	+ +	— —	+ +	— —	+ +	— —	— —	— —	— —
5.2	— —	— —	+ +	— —	+ —	— —	— —	— —	— —
4.9	— —	— —	+ +	— —	— —	— —	— —	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.4	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
5.6	+ +	+ +	. . .	+ +	. . .	+ +	. . .	+ +	. . .
5.2	. . .	+ +	. . .	— —	. . .	(+)(+)	. . .	— —	. . .
4.9	. . .	(+)(+)	. . .	— —	. . .	— —	. . .	— —	. . .

TABLE 5.—*Data Obtained in a Series of Transplants After Administration of Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.2	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.7	+ +	+ +	+ +	— —	+ +	— —	+ +	— —	+ —
5.3	— —	— —	+ +	— —	+ +	— —	— —	— —	— —
5.0	— —	— —	+ +	— —	— —	— —	— —	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.2	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
5.7	+ +	+ +	. . .	+ +	. . .	+ —	. . .	— —	. . .
5.3	— —	— —	. . .	— —	. . .	— —	. . .	— —	. . .
5.0	— —	— —	. . .	— —	. . .	— —	. . .	— —	. . .

TABLE 6.—*Data Obtained in a Series of Transplants After Administration of Calcium Chloride and Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.5	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.6	+ +	+ +	+ +	+ +	+ +	— —	+ —	— —	+ —
5.3	— —	— —	+ +	— —	+ +	— —	— —	— —	— —
4.9	— —	— —	+ +	— —	— —	— —	— —	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.5	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
5.6	+ +	+ +	. . .	+ +	. . .	— —	. . .	— —	. . .
5.3	— —	— —	. . .	— —	. . .	— —	. . .	— —	. . .
4.9	— —	— —	. . .	— —	. . .	— —	. . .	— —	. . .

TABLE 7.—*Data Obtained in a Series of Transplants (No Medicamentation)*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
p_H	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.0	+ +	+ +	+ +	+ +	+ +	+ +	+ +	(+)(+)	+ +
5.5	+ +	+ +	+ +	+ +	+ +	— —	— —	— —	— —
5.2	+ +	+ +	+ +	— —	+ +	— —	— —	— —	— —
4.9	+ +	— —	+ +	— —	+ —	— —	— —	— —	— —
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.0	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .
5.5	. . .	. . .	. . .	. . .	. . .	— —	. . .	— —	. . .
5.2	. . .	. . .	. . .	— —	. . .	— —	. . .	— —	. . .
4.9	. . .	+ +	. . .	— —	. . .	— —	. . .	— —	. . .

TABLE 8.—*Data Obtained in a Series of Transplants After Administration of Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
pH	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.2	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.6	+ +	− −	+ +	− −	+ +	− −	− −	− −	− −
5.3	− −	− −	+ +	− −	− −	− −	− −	− −	− −
4.9	− −	− −	+ +	− −	− −	− −	− −	− −	− −
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.2	. . .	. .	. . .	. .	. .	. .	. .	. .	. .
5.6	. . .	− −	. . .	− −	. .	− −	. .	− −	. .
5.3	+ +	− −	. . .	− −	. .	− −	. .	− −	. .
4.9	+ +	− −	. .	− −	. .	− −	. .	− −	. .

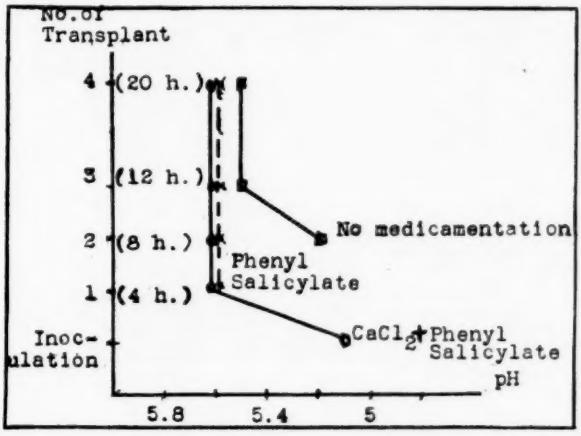

Chart 3.—Curves representing the results in tables 7, 8 and 9.

TABLE 9.—*Data Obtained in a Series of Transplants After Administration of Calcium Chloride and Phenyl Salicylate*

	First Inoculation,	1. Transplant (4 Hours)		2. Transplant (8 Hours)		3. Transplant (12 Hours)		4. Transplant (20 Hours)	
pH	Urine	Urine	Broth	Urine	Broth	Urine	Broth	Urine	Broth
6.2	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
5.6	− −	− −	+ +	− −	− −	− −	− −	− −	− −
5.3	− −	− −	+ +	− −	−(+)	− −	− −	− −	− −
4.9	− −	− −	+ +	− −	− −	− −	− −	− −	− −
	Transplants into Ordinary Broth from Tubes with No Visible Growth								
6.2	. . .	. .	. . .	. .	. .	. .	. .	. .	. .
5.6	+ +	− −	. . .	− −	. .	− −	. .	− −	. .
5.3	− +	− −	. . .	− −	. .	− −	. .	− −	. .
4.9	− −	− −	. . .	− −	. .	− −	. .	− −	. .

TABLE 10.—*Calcium Chloride and Phenyl Salicylate Treatment in Pyuria Due to B. Coli*

Name	Age	Admission; Discharge	Anamnesis	Microscopic Examination of Urine	Bacterial Culture	Daily Dose	No Abnormality on Microscopic Examination of Urine, Days	Urine Sterile, Days	Comment; Complications
D. M. J. D.	57	Oct. 1 Oct. 21	Typical symptoms of pyelitis.....	Leukocytes Bacteria	B. coli	Calcium chloride, 6 Gm. Phenyl salicylate, 4 Gm.	14	14	
J. N.	63	Oct. 29 Nov. 22	Typical symptoms of pyelitis.....	Leukocytes Bacteria	B. coli	Calcium chloride, 5 Gm. Phenyl salicylate, 4 Gm.	8	12	Diabetes mellitus
H. A. K. J.	28	Nov. 2 Dec. 13	Frequent attacks of pyelitis for last six years	Leukocytes Erythrocytes	B. coli	Calcium chloride, 8 Gm. Phenyl salicylate, 4 Gm.	11	30	Parametritis
I. N. H.	23	Dec. 2 Dec. 15	Typical symptoms of pyelitis.....	Leukocytes Erythrocytes	B. coli	Calcium chloride, 5 Gm. Phenyl salicylate, 4 Gm.	18	18	
E. J. H.	9	Dec. 2 Dec. 25	Typical symptoms of pyelitis.....	Leukocytes Bacteria	B. coli	Calcium chloride, 3 Gm. Phenyl salicylate, 2 Gm.	18	18	Pains in stomach after administration of calcium chloride
K. O.	74	Nov. 24 Dec. 30	Painful micturition.....	Leukocytes Bacteria	B. coli	Calcium chloride, 5 Gm. Phenyl salicylate, 4 Gm.	16	28	Chronic polyarthritis
E. S.	9	Dec. 14 Jan. 3	Typical symptoms of pyelitis.....	Leukocytes Crystals	B. coli	Calcium chloride, 3 Gm. Phenyl salicylate, 2 Gm.	16	16	
E. N.	34	Dec. 4 Dec. 29	Tenesmus of bladder; turbid urine..	Leukocytes Crystals	B. coli	Calcium chloride, 6 Gm. Phenyl salicylate, 3 Gm.	19	19	
E. P.	19	Jan. 13 Feb. 4	Typical symptoms of pyelitis.....	Leukocytes Epithelial cells	B. coli	Calcium chloride, 6 Gm. Phenyl salicylate, 4 Gm.	?	?	Pregnancy; symptom-free; discharged on own request
A. G. L.	3	Nov. 26 Jan. 22	Typical symptoms of pyelitis.....	Leukocytes Bacteria	B. coli	Calcium chloride, 2 Gm. Phenyl salicylate, 1 Gm.	14	?	Symptom-free, but —+ growth
E. M. N.	10	May 24 June 15	Pyelitis five times since 1925.....	Leukocytes Rods	B. coli	Calcium chloride, 6 Gm. Phenyl salicylate, 2 Gm.	18	19	

K. P.	10	April 8 May 1	Pyelitis seven years ago; symptoms again	Sediment Rods	B. coli	Calcium chloride, 3 Gm. Phenyl salicylate, 2 Gm.	17	17	
M. B.	35	Feb. 12 Mar. 3	Typical symptoms of pyelitis.....	Leukocytes	B. coli	Calcium chloride, 4 Gm. Phenyl salicylate. 4 Gm.	10	10	
M. M. J.	68	April 24 May 26	Cystitis three years ago; symptoms again	Leukocytes Epithelial cells	B. coli	Calcium chloride, 5 Gm. Phenyl salicylate, 4 Gm.	?	?	
B. E. N.	60	April 20 May 25	Cystitis two times before; symptoms again	Leukocytes Rods	B. coli	Calcium chloride, 4 Gm. Phenyl salicylate, 4 Gm.	?	?	Symptom-free
J. H.	26	June 15 July 2	Persistent cystitis for two years, in spite of treatment	Leukocytes Epithelial cells Rods	B. coli	Calcium chloride, 5 Gm. Phenyl salicylate, 4 Gm. Later, 3 tablets three times daily *	9	9	
I. M. P.	28	June 6	Dyspepsia for last three years; pains in left side	Leukocytes Epithelial cells	B. coli	Three tablets three times daily	10	10	Tuberculous adenitis; dyspepsia
A. S. F.	30	June 18 July 13	Attacks of ureteral colic for last three years	Leukocytes Epithelial cells	B. coli	Three tablets three times daily to three tablets four times daily	18	13	Roentgen examination; no renal calculus
K. M. L.	26	April 16	Periodic pyelitis for several years...	Leukocytes Epithelial cells	B. coli	Three tablets three times daily	? (+ few leukocytes)	8	Exudative pleurisy; no tubercle bacilli in urine
A. M. C.	41	May 12 June 25	Painful urination for several years	Leukocytes Rods	B. coli	Three tablets three times daily	? (+ few leukocytes)	12	Climacterium
E. F.	53	June 27 July 18	Various, indefinite pains; no pains on urination	Leukocytes Rods	B. coli	Three tablets three times daily	15	7	
L. O. M. A.	30	July 5 July 24	Persistent pyelitis postpartum, June 19	Leukocytes Rods	B. coli	Three tablets three times daily	10	10	
K. H.	72	June 25 Aug. 8	Uremia on admission.....	Leukocytes Erythrocytes	B. coli	Three tablets three times daily	?	10	No growth; no tubercle bacilli; leukocytes, +; erythrocytes, +
J. H. M	71	June 17 July 3	Chronic cystitis for many years; heart disease; pulmonary tuberculosis	Leukocytes Rods	B. coli	Three tablets three times daily	?	?	No effect from tablets; discharged after twenty-two days on own request

* The tablets consisted of calcium chloride coated with phenyl salicylate.

In chart 3, it is shown that the effect of phenyl salicylate and that of calcium chloride and phenyl salicylate are mostly parallel; but on one single point the latter method excels. Chart 2 and, at any rate, chart 1 show a more conspicuous difference in the disinfecting power of the urine on the different experimental conditions.

COMMENT

From these experiments it seems evident that, whatever the underlying process may be, the urine gains in disinfecting power when it is kept acid during the treatment with phenyl salicylate. It is possible that some cleavages take place, with splitting of the phenol that is bound to the acids. It cannot be the effect of the acidity itself on the bacteria that sustains the bactericidal effect in the third section of the experimental series; this much is evident from the arrangement of the experiments, as p_H is made to vary to the same extent in all three sections (of the experiments) within each series by the addition of acid or base. And yet, the last section of each series shows a greater disinfectant effect than do the other sections of the respective series, in spite of the same p_H values throughout each series. Some process, then, must have taken place within the organism whereby the disinfecting power of phenyl salicylate is further intensified when the urine is kept acid during the treatment with phenyl salicylate.

This fact, that the disinfecting power of phenyl salicylate is increased by concurrent acidification of the urine, is perhaps something that has been surmised for some time. But, as far as I know, no therapy with phenyl salicylate has previously been instituted against pyuria caused by colon bacilli in which suitable acidity of the urine was made sure of beforehand. These experiments, then, encouraged me to try out a therapy on this basis in patients with pyuria due to *B. coli.*

So I gave the patients calcium chloride—usually 1 Gm.—five times daily till the urine proved acid on a qualitative test with methyl red. The test consists simply in adding two or three drops of a 1 per cent solution of methyl red to about 10 cc. of urine. If the urine takes on a red color, then it has reached a suitable degree of acidity (p_H less than 5.5); if, on the other hand, the urine remains yellow, it is necessary to increase the dose of calcium chloride until the urine is colored red by the indicator.

I have taken care to keep the urine at this degree of acidity by suitable dosage of calcium chloride, while at the same time I have given the patients 1 Gm. of phenyl salicylate four times a day; I have continued this treatment until the catheterized urine proved sterile on culture, which test was made every week.

The results in the patients whom I have treated in this manner are given in table 10 in such a way as to furnish a quick survey of the course of the treatment. In order to avoid the repetitions in giving the details of the various ordinary case histories, I have given only the chief features of each case.

As shown in table 10, the last nine patients received slightly different treatment.

As it was found that the calcium chloride tablets cause cardialgia in some patients and dyspeptic symptoms in others, I thought about the possibility of avoiding this drawback by coating the tablets with phenyl salicylate, so that the calcium chloride would pass through the stomach without undergoing any change.

Considering that phenyl salicylate and calcium chloride are used in somewhat constant proportions in this method of treatment, I communicated with a pharmaceutical firm (Medicinalco, Ltd., Copenhagen) in regard to the possibility of preparing tablets of 0.6 Gm. calcium chloride with a coating of about 0.3 Gm. of phenyl salicylate. After some experimentation, the manufacturers succeeded in producing such tablets. I have treated a number of patients with these tablets, using 3 three times daily for standard doses. Within a few days, the urine would give an acid reaction toward methyl red, just as it did in the earlier treatment with calcium chloride and phenyl salicylate; in a single instance the urine was phenyl salicylate-colored. Dyspeptic conditions developed in no instance, not even on ingestion of 15 tablets a day. One of the patients suffered from dyspepsia beforehand, and his condition was not aggravated during the treatment.

Thus the same effect was attained with these tablets as when calcium chloride and phenyl salicylate were given separately; by this treatment, dyspepsia was avoided altogether. The treatment with pyelol tablets is therefore easy to carry through; it is innoxious, and it can eventually be given as ambulatory treatment. In most of the cases in which it was employed,[9] this treatment resulted in recovery.

SUMMARY

It is shown experimentally that the disinfecting power of phenyl salicylate against *B. coli* is increased by concurrent acidification of the urine.

When calcium chloride and phenyl salicylate were employed together in the clinical treatment of twenty-four patients suffering from pyuria, cures were obtained in 75 per cent.

Calcium chloride alone caused the development of gastric symptoms in some patients, but this was avoided by giving the calcium chloride in tablets coated with phenyl salicylate which contained the proper proportions of both phenyl salicylate and calcium chloride.

9. As these tablets, on account of the coating of phenyl salicylate, pass through the stomach without any discomfort, they are particularly serviceable also in such lesions as bronchial asthma, tetany, urticaria and other conditions with itch of the skin in which one would be inclined to institute a treatment with calcium chloride but forbears to do so on account of dyspeptic troubles.

BENIGN GASTRIC AND DUODENAL ULCERS

CLINICAL DIAGNOSIS AND THE CONDITIONS FOUND AT OPERATION *

HOWARD R. HARTMAN, M.D.
AND
ANDREW B. RIVERS, M.D.
ROCHESTER, MINN.

The more we can learn about peptic ulcer, the more accurate we can be in the recognition of its type, activity and microscopic changes; and the better we understand the complications, the more intelligently we can advise treatment for individual cases.

Surgical treatment for peptic ulcer probably offers the better chance for rapid and permanent cure, particularly in complicated cases, but certain patients respond well to nonsurgical measures and remain entirely without symptoms for an indefinite period. Some patients with peptic ulcers fail to benefit permanently, or perhaps even temporarily, from a medical regimen. In some of these patients the reasons for failure are that the ulcer which is being treated is a penetrating lesion, or perhaps it is one in which obstructive features are easily recognizable. A carefully taken history usually will include information from which fairly accurate deductions regarding the microscopic changes of a lesion can be obtained. Previously it has been pointed out by one of us (Rivers [1]) that patients with ulcer, who have severe epigastric pains, especially if these pains are referred through to the back, or upward into the chest, are likely to do poorly on a nonsurgical regimen. Patients with such symptoms usually have a perforating type of lesion, and as a rule, they come to operation before permanent relief is obtained.

Another pitfall which usually can be avoided by taking a careful history is failure to recognize other pathologic entities which may exist in conjunction with a peptic lesion. It is obvious that the nonsurgical treatment of ulcer, under such circumstances, usually would be a waste of time and a great injustice to the patient. It is common knowledge that peptic ulcer often is found in conjunction with varying degrees of cholecystitis and appendicitis. Although this "trinity of disease" is far from unusual, one or the other pathologic entity is almost certain to demand especial consideration in diagnosis because of the predominant grouping of pertinent symptoms. Peptic ulcer may be present, and

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* From the Division of Medicine, the Mayo Clinic.

1. Rivers, A. B.: New Developments in the Treatment of Peptic Ulcer with Notes on the Preoperative Care and Management of Complications, Journal-Lancet **48**:21, 1928.

there may be definite characteristics in the history suggesting that it is active, yet concurring secondary conditions ultimately may prove of great importance, and the apparently dominating condition may respond differently to therapeutic attempts because of variations in the importance of the secondary condition.

Smithies,[2] in reviewing the observations following laparotomy in 264 cases of gastric ulcer, stated: "In 35 per cent of instances, diseased appendix was associated with gastric ulcer. In 15 per cent cholecystitis and cholelithiasis were demonstrated as concomitant processes. In view of these figures, it is evident that all laparotomies should be thoroughly explored even when a well marked gastric ulcer has been demonstrated." Smithies also found as associated lesions, Lane's kink twice, carcinoma of the gallbladder once and pancreatitis four times. Eusterman,[3] in reviewing a series of surgically verified gastric and duodenal ulcers, found that associated disease in the appendix occurred in 40 per cent and in the gallbladder in 9.7 per cent.

PURPOSE OF STUDY

In glancing over a large series of histories of cases in which the preoperative diagnosis is gastric or duodenal ulcer, one is impressed with the variety of associated diseases that is found at operation. Many problems immediately present themselves, and about a few of them we decided to gather information with the following purposes in mind: (1) to acquaint ourselves with the diseases that may be hidden in the ulcer syndrome sufficiently to pass unrecognized in the preoperative observation of the clinicians and the consulting surgeons; (2) to determine whether more careful evaluation of symptoms and observations, with probable greater accuracy in detection of associated diseases, would materially benefit the patient; (3) to answer, if possible, the question as to whether the probability of coexisting disease should influence us in advising surgical treatment for a patient with an ulcer which we believe would respond well to a medical regimen, and (4) to focus our attention on the rarer associated diseases, giving brief illustrative case histories to see if by any signs we could have suspected the pathologic changes encountered at operation.

MATERIAL

The material for study included the records of 1,075 patients in whom ulcerating lesions of the stomach and duodenum were found at

2. Smithies, Frank: Gastric Ulcer Without Food Retention: A Clinical Analysis of One Hundred and Forty Operatively Demonstrated Cases, Am. J. M. Sc. **161**:340, 1913.

3. Eusterman, G. B.: The Essential Factors in the Diagnosis of Chronic Gastric and Duodenal Ulcers, J. A. M. A. **65**:1500 (Oct. 30) 1915.

operation. A prerequisite to inclusion of these histories in the series was that the diagnosis of a single lesion, such as gastric ulcer or duodenal ulcer, must have been made preoperatively. Histories of cases in which a dual diagnosis, such as gastric ulcer and cholecystitis, was made by the clinician were not accepted for study. Cases in which another condition was diagnosed that was irrelevant to the condition in the stomach or duodenum, for instance, a case with the diagnosis of duodenal ulcer and hypertrophic arthritis of the right knee, were not excluded from this series. The pathologists' reports were taken as the final diagnosis when the tissues were removed. In a great number of these cases, however, tissue was not removed; in these, the surgeon's diagnosis was accepted.

This series of 1,075 cases included 700 of duodenal ulcer and 375 of gastric ulcer.

LESIONS FOUND IN PATIENTS OPERATED ON FOR DUODENAL ULCER

Chart 1 is a graphic representation of the various lesions found at operation after a clinical diagnosis of duodenal ulcer had been made. The data were compiled from a study of 700 cases. In 38 per cent, duodenal ulcer was the sole abnormality found at operation. In 62 per cent, some pathologic entity not specified preoperatively was found to be associated with the peptic ulcer. The diagnosis of diseased appendix was made by the operating surgeon in 51.8 per cent of the cases; in only 7.4 per cent, however, was the appendix acutely or subacutely inflamed. Hence, 14.3 per cent of all cases of appendicitis found in patients operated on for ulcer of the duodenum seems to have been of noteworthy significance. In 3.6 per cent of the 700 patients, distinct cholecystitis also was found. An associated ulcer in the stomach was noted in 3.6 per cent of the cases from which this chart was compiled. A rather curious fact is that this small group included eight cases (1.1 per cent included in the miscellaneous group) in which gastric ulcer was found after the clinician, basing his diagnosis of position of the lesion mainly on the roentgen data, had made a diagnosis of duodenal ulcer. There is a miscellaneous group of 3 per cent. Among the more unusual observations are: duodenitis without actual ulcer, 0.7 per cent; benign tumors, 0.4 per cent; Meckel's diverticulum, 0.3 per cent; duodenal diverticulum, 0.14 per cent, and one of carcinoma of the stomach, 0.14 per cent. Attention should be called here to the fact that in 700 operations for duodenal ulcer, only once was a carcinoma discovered.

LESIONS FOUND IN PATIENTS OPERATED ON FOR GASTRIC ULCER

Chart 2 represents graphically the lesions found at operation after a preoperative diagnosis of gastric ulcer had been made. It will be

noted that in a little more than half of these patients, 50.8 per cent, a lesion other than the gastric ulcer was not discovered. Associated appendicitis was reported by the surgeon in 38.8 per cent of these cases. Of this group, however, in only 3.1 per cent was the appendix in a state of subacute or acute inflammation. Duodenal ulcer in association with gastric ulcer was found twenty times, or 5.2 per cent. Cholecystitis was found eight times, or 2.1 per cent. Probably the most important fact which is apparent from a study of these data is that

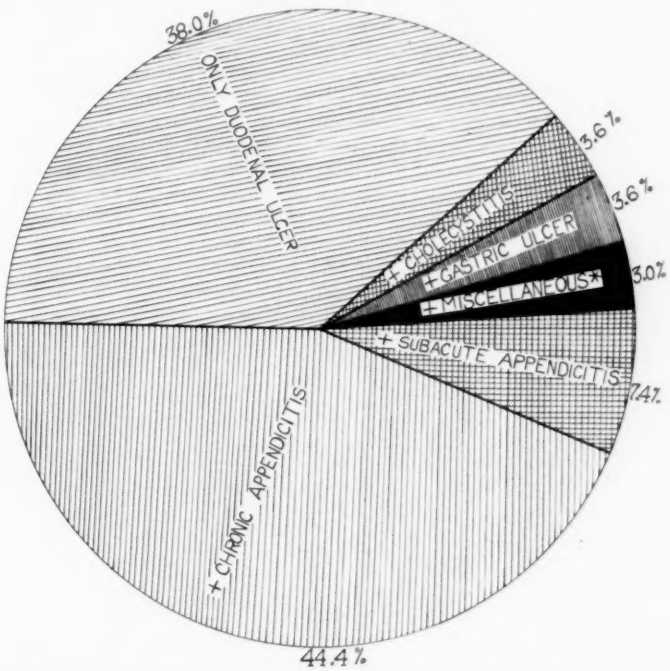

Chart 1.—Percentage of lesions found at operation after duodenal ulcer had been diagnosed clinically. In the section designated miscellaneous are included: gastric ulcers only, 1.1 per cent; duodenitis only, 0.7 per cent; benign tumors, 0.4 per cent; Meckel's diverticulum, 0.3 per cent; duodenal diverticulum, 0.14 per cent, and associated carcinoma of the stomach, 0.14 per cent.

changes which aroused suspicion of a malignant condition were found in 2.1 per cent of these ulcers. The more unusual lesions discovered in the course of laparotomy on patients included in this group were Lane's kink in 0.26 per cent; calcareous lymph node of the jejunum, in 0.26 per cent; splenitis, in 0.26 per cent, and gastritis without pathologic evidence of gastric ulcer in 0.26 per cent.

LESIONS FOUND IN PATIENTS OPERATED ON FOR EITHER DUODENAL OR GASTRIC ULCER

Chart 3 represents a combination of chart 1 and 2. These cases have been subdivided into four groups. The groups will be considered separately.

Group 1.—This includes (*a*) cases in which only the gastric or duodenal ulcer preoperatively specified was found; (*b*) cases in which

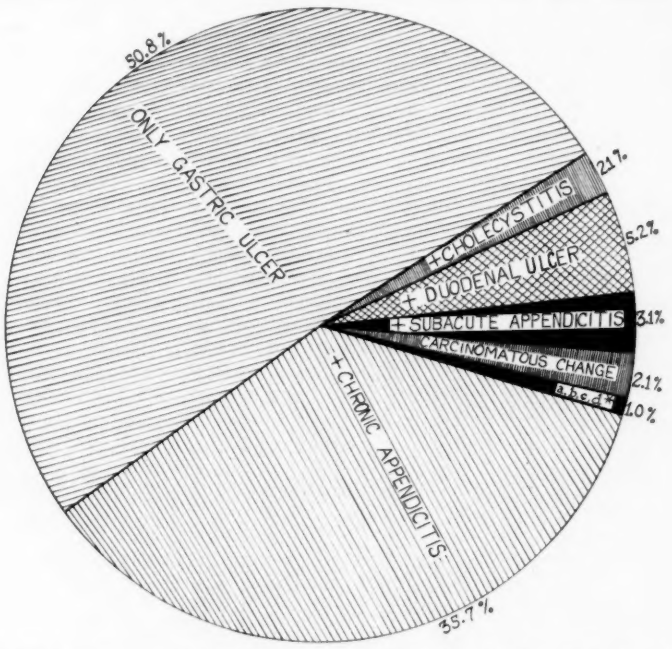

Chart 2.—Percentage of lesions found at operation after gastric ulcer had been diagnosed clinically. In the section designated a, b, c, d, are included: Lane's kink, 0.26 per cent; cancerous gland of the jejunum, 0.26 per cent; gastritis only, 0.26 per cent, and splenitis, 0.26 per cent.

both duodenal and gastric ulcers were found; (*c*) cases in which, in addition to ulcer, chronic appendicitis was found.

In 42.3 per cent of the total number of cases included in this group, operation revealed only the pathologic condition diagnosed by the clinician. Furthermore, the lesion was found in the location indicated preoperatively. In forty-six instances, or 4.2 per cent, both duodenal and gastric ulcer were discovered at operation. Frequently there were multiple ulcers in the stomach or duodenum. This becomes of some importance when one considers that the surgeon who is satisfied with

only the ulcer which already has been found, and fails to explore further, may overlook secondary ulcers. Thus, a situation may arise which is extremely unpleasant for the patient and embarrassing for the surgeon. In the cases diagnosed as gastric ulcer, combined ulcers were found a little more frequently than in those with the diagnosis of duodenal ulcer. In 3.6 per cent of the cases diagnosed as duodenal

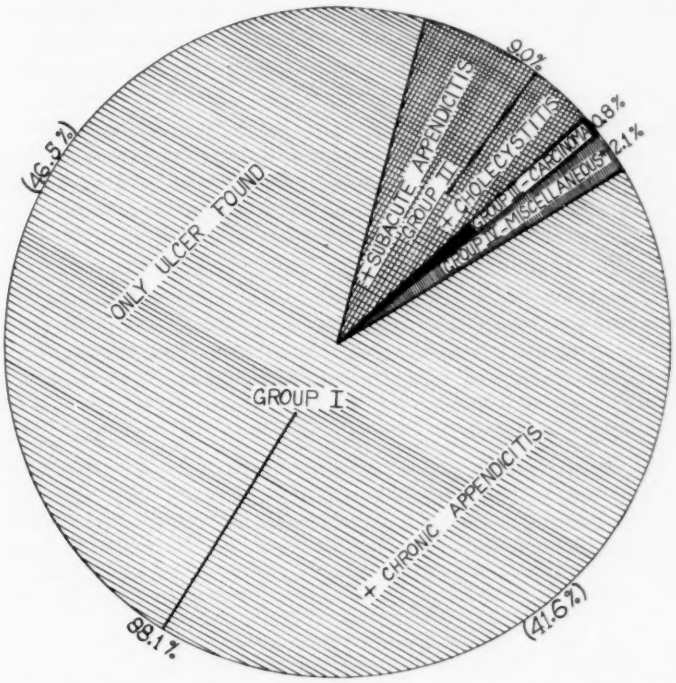

Chart 3.—Percentage of lesions found at operation, arranged in groups, after duodenal ulcer and gastric ulcer had been diagnosed clinically. In the section designated miscellaneous are included: benign tumors, 0.3 per cent; duodenitis or gastritis, 0.5 per cent; diverticula, 0.3 per cent; Lane's kink, calcerous gland of the jejunum, and splenitis, one case each, 0.3 per cent, and opposite ulcer, 0.7 per cent.

ulcer, gastric ulcer also was present, whereas in 5.2 per cent of those diagnosed as gastric ulcer, combined ulcer was present. The lesion most frequently associated with peptic ulcer is a chronically inflamed appendix. Forty-one and six-tenths per cent of the patients sent to operation with a diagnosis either of gastric or of duodenal ulcer were found to have chronic appendicitis also.

The frequency of appendicitis deserves some comment. At the usual ulcer age there are, as a rule, some chronic inflammatory changes in all appendixes. Carnett [4] expressed the opinion that the appendix in practically every adult shows some evidence of previous inflammation. It is customary at the Mayo Clinic to remove all appendixes whenever practicable during the course of the less complicated laparotomies. This procedure has, of course, certain limitations enforced by age, the general condition of the patient, emergency operation and other conditions. In the ulcer group usually there are no contraindications to secondary operative procedures such as appendectomy. Removal of the appendix does not materially increase the risk of the operation, and such a procedure may save the patient another operation at a later date. The importance of associated appendicitis, however, should not be overestimated. There is some doubt that a mildly inflamed appendix will cause gastro-intestinal symptoms of any great importance. These patients obviously did not make a serious complaint referable to the lower right quadrant, or some suggestion of the possible coexistence of this lesion would have been included in the consulting physician's résumé of the case.

The argument advanced by certain surgeons and pathologists for the routine removal of appendixes encountered during laparotomy is that the appendix may become a focus of infection, thus disseminating disease elsewhere through the abdomen. Regarding this, Carnett and Boles [5] have the following to say:

> Many of the theories relative to chronic appendicitis causing distant lesions originated before it was realized how commonly the appendix shows gross or microscopic evidence of chronic changes due to normal evolution of the organ. The fairly constant findings of alterations in every appendix removed coincident with operations on the stomach, duodenum or gallbladder are not to be regarded as cause and effect. The same changes are noted in appendixes removed incidental to operation on pus tubes or right inguinal hernias. Aberrant or retrograde lymph flow from a chronically diseased appendix might, therefore, just as logically be ascribed as the cause of pus tubes or right inguinal hernia as of gastric ulcer or biliary disease. There is no doubt that toxins and bacteria carried in the portal circulation may cause pathologic change in the liver or gallbladder, but there is no good reason to believe that these noxious agents originate in a comparatively small sclerosed appendix rather than elsewhere in the large sewage system of the intestinal tract.

Group 2.—In this group are included cases in which in addition to peptic ulcer, acute or subacute appendicitis or cholecystitis was present.

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4. Carnett, J. B.: Chronic Pseudoappendicitis Due to Intercostal Neuralgia, Am. J. M. Sc. **174**:579, 1927.

5. Carnett, J. B., and Boles, R. S.: Fallacies Concerning Chronic Appendicitis, J. A. M. A. **91**:1679 (Dec. 30) 1928.

Acute or subacute appendicitis was found unexpectedly as an associated lesion complicating peptic ulcer sixty-three times, or 5.9 per cent, in 1,075 operations. This complication, it will be recalled, was discovered in patients operated on for duodenal ulcer in 7.4 per cent of 700 cases. It is interesting that of the patients on whom operation was performed for gastric ulcer, only 3.1 per cent were found to have definite inflammation in the appendix. The greater prevalence of this complication in those patients who were operated on for duodenal ulcer probably finds some explanation in the fact that these patients are usually younger, and thus are more likely to be in that period of life when acute appendicitis is most common. That the presence of acute or subacute appendicitis should have remained undetected in these patients is rather strange. Of course, even severe appendicitis may give few, if any, symptoms, and may even go on to rupture without causing much pain. There is the possibility, also, that patients who are having enough distress from peptic ulcer to cause them to undergo operation might ignore the presence of less severe pain in the lower right quadrant and thus might fail to complain of distress in that area. The pain of appendicitis is not infrequently situated just to the right and but very slightly below the level of the umbilicus. Undoubtedly, therefore, even though the patient might complain of pain in this area it might be assumed that peptic ulcer would explain this also. Our experience leads us to believe that a patient with gastric or duodenal ulcer rarely localizes his pain in an area which could be confused with that of an inflamed appendix. Almost invariably the patients who are found at operation to have an appreciable degree of appendicitis will have an area of definite tenderness easily distinguishable from that usually expected in patients who have ulcer alone. In spite of what can be brought forward in defense of the examining physician who fails to suggest definite disease in the appendix, even in the presence of a known peptic ulcer, there is reason to suspect that he was hasty in his examination of the abdomen or that he was too easily satisfied with the diagnosis of the case when the roentgenologist reported finding deformity in the stomach or duodenum.

Cholecystitis in addition to a gastric or duodenal lesion was discovered at laparotomy in 3.1 per cent of the cases in which the clinical diagnosis had been either gastric or duodenal ulcer. It will be recalled that when cases in which the diagnosis was gastric ulcer were being considered in a class by themselves, disease of the gallbladder was found in 2.1 per cent. Similar consideration of the patients on whom operation was performed after a diagnosis of duodenal ulcer was made showed that in 3.6 per cent the gallbladder was sufficiently diseased to justify its removal. An error of 3.1 per cent in this group is surprisingly low, particularly when it is considered that the symptoms of

cholecystitis and peptic ulcer may be difficult to differentiate. It is doubtful if, with the help of meticulously taken histories and added experience with cholecystography, we shall be able to improve much on this figure.

Group 3.—This group includes cases of malignant lesions, and lesions suspected of being malignant which were found in the course of laparotomy performed after a preoperative diagnosis of gastric or duodenal ulcer. Because of the importance of this complication, we are submitting for analysis the individual histories of all of the eleven patients in this group; in all but one, the preoperative diagnosis was gastric ulcer.

In the first two cases, specimens removed were diagnosed microscopically as carcinoma, and this leaves no doubt that the lesions were malignant.

CASE 1.—A man, aged 62, had had intervals of dyspepsia for twenty-five years. He had suffered from pain in the midepigastrium which had come on two hours after meals. Frequently pain had awakened him at 3 a. m. Sodium bicarbonate had relieved him although for a short time previous to his admission to the clinic, relief had not been complete. He had had daily distress for six months. During this time he had noticed a loss of weight of 6.8 Kg. During the month before admission, he frequently had avoided food for two or three days because then he was more comfortable. He was examined in the clinic. Gastric analysis[6] revealed total acids 60, free hydrochloric 42 and total content recovered 1,000 cc. The report of the roentgenologist was duodenal ulcer with obstruction. After preoperative preparation, operation was performed. On the duodenal side of the pylorus was an ulcer; on the gastric side, a perforating carcinoma.

This is the only case included in our series in which the diagnosis was duodenal ulcer and in which a malignant condition was found at operation. Carcinoma of the duodenum is so rare that its differential diagnosis needs scarcely be considered in dealing with duodenal ulcer. In this instance, the marked obstruction was perfectly evident to the roentgenologist, but the area of malignancy, which was near the pylorus on the gastric side, was not visualized. By general examination, one would have been unable to detect the carcinoma, and there was nothing in the history to suggest such a complication. The history of a disturbance of twenty-five years' duration is characteristic of ulcer. The recent change in symptoms was due to obstructive features being superimposed on those caused by the old ulcer. Either the ulcer or the carcinoma may have caused the obstruction.

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6. In each instance throughout this paper, the quantitative expression of acidity of gastric contents is in terms of number of cubic centimeters of tenth normal solution of sodium hydroxide required to neutralize 100 cc. of gastric contents. The quantity reported as the content recovered is obtained one hour after the test meal has been given.

CASE 2.—A woman, aged 51, had had pain in the upper portion of the abdomen for one month. Pain came on about one hour after the meal, and radiated upward into the left side of the chest. There was much gas, belching and regurgitation of acid gastric contents. She vomited at intervals. Distress was worse when the stomach was empty. Occasionally she was awakened at night by pain in the epigastrium. Analysis of gastric contents revealed total acidity ranging from 12 to 24 and persistent achlorhydria; the quantity of content recovered was 247 cc. The report of roentgen examination was that pyloric spasm and a suggestion of a small gastric ulcer were present. At operation, early carcinoma on the border of a gastric ulcer was found.

Roentgen observations in this case did not help much except to localize the lesion. Clinically, however, there was much evidence which might have led one to suspect the presence of a complicated gastric ulcer. The age of the patient, the short history and the persistent anacidity should have made the clinician suspicious of the presence of a malignant ulcer or early carcinoma. A history of the ulcer type is not at all uncommon in a malignant condition. Often these patients complain of pain which comes on late after eating, and which is promptly relieved by the ingestion of food or soda. This is particularly true of the penetrating types of carcinomatous ulcers. On the other hand, the brevity of the history and the anacidity are not entirely inconsistent with the diagnosis of benign gastric ulcer. Usually, however, ulcers do not cause the severe symptoms manifested in this case.

In the following nine cases, the opinion of the surgeon, based on the gross pathologic appearance of the lesions at operation, was that a malignant condition was present. The gross pathologic appearance at times is deceptive, and further proof of the probability of diagnostic error in some of these patients is the fact that they are alive many years following the laparotomy at which the ulcer could not be excised.

CASE 3.—A woman, aged 53, had suffered from dyspepsia for about fifteen years. During the first twelve of these years, trouble had been intermittent. During the last three years, she had had almost daily distress. Pain had come on between meals, but had been relieved promptly by the taking of sodium bicarbonate. Occasionally she had had nausea and vomiting with the pain, and occasionally she had vomited small amounts of blood. On a few occasions there had been severe crampy, epigastric pains. On the administration of a test meal, there was total acidity of 32 and free hydrochloric acid of 22; the quantity of gastric contents recovered was 148 cc. Roentgen examination disclosed a perforated gastric ulcer with hour-glass deformity. At operation, subacute perforating gastric ulcer with hour-glass contraction was found. The lesion looked malignant.

This patient's dyspepsia began when she was 38 years of age and continued for twelve years with the usual characteristics of ulcer. Then she began to have daily trouble, still with characteristics of ulcer, but with nausea and vomiting. At operation, a perforating ulcer with hour-glass contraction was found; the perforation probably was related

to the hour-glass contraction as cause to effect. Either of these complications could cause a slight change in symptoms. The symptoms of hour-glass stomach are not very definite; but usually, after this complication develops, the symptoms of nausea and vomiting supervene on the already established syndrome of ulcer.

CASE 4.—A man, aged 64, had begun to have trouble with his stomach thirteen years prior to the time when he was seen at the clinic. Epigastric distress had come on at any time; meals frequently had aggravated it, and vomiting had come on at irregular intervals. He had been troubled with much belching and bloating. Eleven years previously he had had severe epigastric pain, and an emergency operation had been done. A gastric ulcer had been found and sutured. Following this, the patient had been fairly well for more than ten years. Then recurring symptoms like those experienced before the operation had developed. On gastric analysis there were found total acidity of 64, free hydrochloric acid of 36 and total quantity of 260 cc. Roentgen examination disclosed a perforated ulcer, on the lesser curvature, near the pylorus. At operation, a gastric ulcer was found which had perforated to the pancreas. The surgeon believed the ulcer to be carcinomatous.

In this case the ulcer had perforated eleven years prior to examination at the clinic. Emergency operation had been necessary to suture the perforation. For ten years thereafter the patient had felt well. Frequently perforation or brisk hemorrhage is followed by complete subsidence of dyspepsia or at least by a prolonged interval of freedom from symptoms.

CASE 5.—A man, aged 38, for several years had had a sensation of much fulness, belching and slight pain coming on from two to three hours after his meals. He had spit up sour material several hours after eating. Pain at times had been referred from the epigastrium to the chest and back. On gastric analysis, total acidity had been found to be 70, free hydrochloric 48 and total quantity 150 cc. Deformity high on the lesser curvature had been found on roentgen examination. Operation revealed, high on the lesser curvature, an ulcer which was perforating to the pancreas. The operating surgeon believed the ulcer was malignant.

This patient gave a history that is not unusual in gastric ulcer. The pain in this instance was referred from the epigastrium upward into the chest and through to the back. This is usually significant of a penetrating lesion. The direction of reference of pain may be the same whether the lesion is gastric or duodenal. The ulcer in this case was found to have perforated to the pancreas.

CASE 6.—A man, aged 45, came to the clinic complaining of dyspepsia which dated back twenty years. This is a definite characteristic of ulcer. During the last month the pain had been more severe. Frequently it had been referred through to the back and had been so severe it had doubled him up. He had obtained imperfect easing of symptoms by taking food or sodium bicarbonate. There had

been a recent loss in weight of 4.5 Kg. A large, perforating gastric ulcer was revealed by roentgen examination. This, at operation, was thought to have undergone malignant change.

Nothing suggestive of a malignant condition was found in this history. The symptoms started when the patient was 25 years of age. There were the usual characteristics of ulcer. The failure to get perfect ease from symptoms after ingestion of food or sodium bicarbonate is not unusual in the perforating types of ulcer. The ulcer was large, and it may have [7] been because of this that the diagnosis of malignancy was made. MacCarty has pointed out that chronic ulcers, whether simple or carcinomatous, vary greatly in size, shape and form. As a rule, most chronic gastric ulcers larger than 2.5 cm. in diameter are carcinomatous. This complication is less frequent in subacute perforating ulcers.

Case 7.—A man, aged 50, had had intermittent dyspepsia for eight years, with fewer periods of freedom lately. Distress had consisted of severe sharp, burning epigastric pain which had come on about two hours after meals and which had been relieved by the taking of food. Occasional vomiting, not of the retention type, had occurred. He had been severely constipated. In six years he had lost 18.1 Kg. in weight. On gastric analysis, total acidity was found to be 56, free hydrochloric acid 36 and the total quantity of gastric contents 185 cc. Roentgen examination revealed a large perforated ulcer on the lesser curvature, at the middle portion of the stomach. At operation, a large perforated ulcer was found which was thought to be malignant.

Case 8.—A man, aged 44, had had intermittent dyspepsia for nine years. Three years prior to examination at the clinic he had had an operation for ulcer of the stomach. He had been better following this, until two and a half months before he was seen at the clinic. During this two and a half months he had had epigastric distress at intervals, and at times severe pain which had been referred through to the back, and which had attained maximal intensity from one to one and a half hours after meals. He had had some headache and dizziness and had been severely constipated. Roentgen examination revealed a small ulcer high on the lesser curvature of the stomach. At operation a subacute gastric ulcer, probably malignant, was found.

Case 9.—A man, aged 54, had had dyspepsia for five years. Sometimes he had been comfortable for three or four weeks. From one-half to three hours after meals he had suffered from burning epigastric pain which had been relieved by the taking of food. He had not tried sodium bicarbonate. He had been nervous, had suffered some loss of weight and had been badly constipated. A large, perforated gastric ulcer, high on the lesser curvature, was evident by roentgen examination. At operation a perforating gastric ulcer was found which was too high to remove. Gastro-enterostomy was performed. The lesion looked malignant.

The three preceding cases can be considered collectively because the histories and operative observations are similar. The symptoms date back for from five to eight years and have the usual characteristics of

7. MacCarty, W. C.: Chronic Ulcer and Carcinoma of the Stomach, Am. J. M. Sc. **173**:466, 1927.

ulcer: intermittency, onset of pain late after meals and relief from the taking of food and sodium bicarbonate. In two instances, the ulcer was high on the lesser curvature; in the other instance, it was near the angle. The operating surgeons were of the opinion that the lesions were malignant, but specimens were not removed for diagnosis, and the data used as criteria of a malignant condition were not stated.

CASE 10.—A man, aged 54, had had dyspepsia for six months, epigastric pain one and a half hours after meals and pain which waked him at night. He had obtained relief by the use of food and sodium bicarbonate. In two attacks of severe pain in the epigastrium, hypodermic medication had been required. After a test meal, total acidity of the gastric contents was 54, and free hydrochloric acid, 34; the quantity of content was 75 cc. Roentgen examination disclosed a perforated ulcer on the lesser curvature. At operation, a large ulcer on the lesser curvature, probably malignant, was found.

CASE 11.—A man, aged 64, had had dyspepsia dating back ten months. There had been epigastric pain radiating into the chest, which had been relieved by the taking of food and sodium bicarbonate. He had suffered from much flatulence. Rarely, he had vomited sour material. There was qualitative food relationship. Sweets and fats had caused trouble. The results of gastric analysis were as follows: total acidity, 52; free hydrochloric acid, 32; quantity, 70 cc. A large, perforated gastric ulcer was revealed by roentgen examination. At operation an ulcer, probably malignant, was found.

In both of these cases, the history of dyspepsia was short, dating back ten months in one instance and six months in the other. Both patients were in the cancer age. In one instance, the history had all the characteristics of a rather severe penetrating type of peptic ulcer. The only suggestion of a malignant condition lay in the fact that symptoms of dyspepsia did not arise until the patient was 54 years of age. Too much significance should not be placed on the fact that dyspepsia does not begin until after the age of 50. It is not particularly unusual for symptoms which prove at operation to be due to a benign gastric ulcer to arise after that age. In case 11, there were symptoms which are more suggestive of a malignant condition than of benign ulcer. This patient had not had trouble with her stomach until the age of 63. There was some relief from pain by ingestion of food or sodium bicarbonate. This is not an uncommon experience of patients with carcinoma. There was much nausea and some vomiting. These symptoms were worse after the taking of sweets or fats.

Several facts stand out rather prominently after considering this group. In the first place, only one carcinoma was found in 700 cases in which the preoperative diagnosis of duodenal ulcer was made. In the gastric ulcer group, however, things were different. Although carcinoma was proved in only one of these cases it was suggested in some of the others. It is impossible to be absolutely certain preoperatively that any gastric ulcer is benign.

Group 4.—Some of the lesions less commonly associated with ulcer in laparotomies undertaken after a clinical diagnosis of gastric or duodenal ulcer had been made are included in this group. The relative frequency of these lesions was found to be as follows: benign tumors, 0.3 per cent; duodenitis or gastritis, 0.5 per cent; diverticula, 0.3 per cent; miscellaneous, Lane's kink, splenitis and calcareous lymph node of the jejunum, one case each, 0.3 per cent; cases in which the opposite ulcer was found, 0.7 per cent. In three cases, benign tumors were present.

Case 12.—A woman, aged 30, for eight months prior to admission to the clinic had had attacks of severe pain in the upper part of the abdomen which had radiated from the epigastrium through to the left shoulder and for relief of which hypodermic medication had been necessary. Flatulence, nausea and vomiting had been associated with the pain. Attacks usually had come on suddenly, had lasted a few hours and had disappeared. Five months before coming to the clinic the patient had been operated on for disease of the gallbladder. At operation, the gallbladder was found to be normal in every way. On gastric analysis, total acidity was found to be 48, free hydrochloric acid, 28 and the quantity of gastric contents, 80 cc. A duodenal ulcer was revealed by roentgen examination. At operation a small ulcer, just below the pylorus on the anterior wall, chronic appendicitis, and a large pancreatic cyst adherent to the entire posterior surface of the stomach were found. The pressure of this large tumor on the posterior wall of the stomach can be seen plainly in the roentgenogram that was made before the operation.

The symptoms in this case are not those usually attributable to peptic ulcer. The ulcer was probably not the cause of the complaints of the patient. In this instance, reconsideration of the roentgenogram of the stomach disclosed the imprint of the tumor on the posterior wall of the stomach. If, in addition to the clinical history, this information had been available preoperatively, a correct diagnosis probably would have been possible. Unless a fluctuating tumor about the umbilicus is demonstrable, however, the diagnosis of a pancreatic cyst is extremely difficult. Even when a tumor is palpable, it may be difficult and frequently is impossible to be certain that its origin is pancreatic. Mesenteric cysts, tumors of the kidney or spleen, retroperitoneal tumors, and even ovarian cysts may be so difficult to differentiate, that the question cannot be settled by means of palpation and the most carefully taken history. Judd[8] reviewed records of forty-one pancreatic cysts at the Mayo Clinic. Regarding the complaint registered by these patients, he stated:

The symptoms of the cyst usually are recorded as due to its pressure on adjoining organs. Pain is nearly always present and in our series of cases was more pronounced than in most of those formerly reported. If the tumor becomes

8. Judd, E. S.: Cysts of the Pancreas, Minnesota Med. **4**:75, 1921.

large, it presses on the stomach causing indigestion and vomiting. Some of our patients had severe seizures of vomiting which we attributed to accompanying pancreatitis rather than to pressure. Pressure may be exerted on the diaphragm, colon and bile ducts. Jaundice is not usually present in these cases. Loss of weight was considerable in many instances.

Judd further pointed out the frequent relationship of cholecystitis and pancreatic cysts.

CASE 13.—A man, aged 33, for eleven years had had long intervals of mild dyspepsia. He had the sensation that there was a lump in the stomach, and much fulness and bloating. The first pain, with characteristics of ulcer, had come on four years previous to examination. He had obtained ease with food and sodium bicarbonate. Night pain and melena had appeared two years prior to examination. The pain was located in the midepigastric region, and on a few occasions had been very acute. On gastric analysis, the total acidity was found to be 76, and free hydrochloric acid, 56; the quantity of contents recovered was 120 cc. Roentgen examination revealed duodenal ulcer, and operation, in addition to the duodenal ulcer, revealed chronic appendicitis and a pedunculated fibroma of the jejunum.

In this case the discovery of a pedunculated fibroma of the jejunum was unexpected. The history was that of ulcer, and there were no symptoms which would have led any one to suspect the lesion which was found. Fibroma of the jejunum is an extremely rare condition. These tumors may grow into the lumen of the bowel or may push outward. The tumors which grow inward usually are small, but because of this position they may cause intestinal obstruction. The fibromas of the intestines which extend outward may become very large. Grossman[9] reported one arising from the transverse colon that reached the size of a man's head.

CASE 14.—A man, aged 39, had had a complaint of the ulcer type for eleven years. Intervals of epigastric pain and tenderness had come on late after meals or had waked him at night. He had obtained some ease by the use of food and sodium bicarbonate. He had suffered from much nausea and bloating but not from vomiting. Gastric analysis revealed total acidity of 68 and free hydrochloric acid, 50; the quantity of stomach contents recovered was 100 cc. Roentgen examination disclosed a duodenal ulcer. At operation, a duodenal ulcer and chronic appendicitis were found; a cystic tumor, which grew from the suspensory ligament of the liver, was also discovered.

The symptoms in this case were undoubtedly caused by the ulcer. There was nothing in the history nor in the general examination that might have suggested the presence of a cystic tumor which was found to have grown from the suspensory ligament.

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9. Grossman, Paul: Quoted by Reichel, Paul; and Staemmler, Martin: Die Neubildungen des Darmes, Stuttgart, Ferdinand Enke, 1924, p. 258.

In 700 cases diagnosed as duodenal ulcer, preoperatively, duodenitis was found in five and gastritis in one. In the 450 cases in which operation was performed for gastric ulcer, gastritis was found only once.

CASE 15.—A man, aged 32, for eighteen months had had intervals of dyspepsia lasting from two to three days. He described a dull pain in the epigastrium and right upper quadrant of the abdomen, associated with nausea and flatulence which came on from fifteen to thirty minutes after eating. There was a burning sensation in the stomach, eructation of gas and vomiting of small amounts of food shortly after eating. He was severely constipated. His symptoms had been gradually progressive. On gastric analysis, total acidity was found to be 94 and free hydrochloric acid, 74; the total quantity of gastric contents was 120 cc. Duodenal ulcer was found on roentgen examination. At operation, chronic appendicitis and an area of duodenitis were discovered. The gallbladder was normal.

CASE 16.—A man, aged 40, had had dyspepsia for four years, with much belching and bloating after meals. Cabbage and turnips had caused him trouble. On two occasions he had had colicky pain in the upper part of the abdomen with residual soreness. During the year before admission to the clinic, epigastric pain had come on two hours after eating and had been relieved by the taking of sodium bicarbonate. On gastric analysis total acidity was found to be 68 and free hydrochloric acid, 48; the total quantity of gastric contents was 100 cc. The roentgen diagnosis was duodenal ulcer. Operation revealed chronic appendicitis and an area of duodenitis. The gallbladder was normal.

CASE 17.—A man, aged 37, complained of periodic dull aching in the epigastrium coming on two hours after meals. The pain never was severe. Occasionally there was nausea but no vomiting. For several years he had had some anorexia and spells of dizziness. The blood count was within normal limits. Gastric analysis disclosed the following: total acidity, 88 and free hydrochloric acid, 76; a total of 80 cc. of gastric contents was expressed. Duodenal deformity was disclosed at roentgen examination. The diagnosis was peptic ulcer, and at operation extensive duodenitis associated with multiple ulcers and chronic appendicitis was found. Duodenitis was found in resected tissue.

CASE 18.—A woman, aged 62, had stomach trouble that had begun about a year previously. Two or three hours after meals she experienced an uncomfortable sensation of fulness which was relieved somewhat by the taking of sodium bicarbonate. She had slight pain just above the umbilicus which seemed "to go through her to the back." Fried foods made her symptoms worse. She had had much nausea and some vomiting, and she was constipated. Gastric analysis revealed total acidity of 80 and free hydrochloric acid of 60; the total quantity of stomach contents was 70 cc. Duodenal deformity was found at roentgen examination. The diagnosis was duodenal ulcer. At operation, a small duodenal ulcer and a considerable amount of duodenitis were found. The appendix gave evidence of chronic inflammation.

CASE 19.—A man, aged 39, had had stomach trouble at intervals for nine years. He had pain in the midepigastrium which, late after eating, was severe and at times was colicky. Distress was frequently referred through to the back, and it was relieved by the taking of food and sodium bicarbonate. Three years before he came to the clinic, an ulcer had perforated the wall and the place had been sutured. Shortly after this operation dyspepsia of the ulcer type had again

developed. At intervals he had had hemorrhages. Roentgen examination disclosed duodenal ulcer. At operation chronic appendicitis, duodenal ulcer and an area of duodenitis were found.

In cases 15 and 16, definitely punched-out ulcers were not found at operation. Instead, an area of localized inflammation of the duodenum was apparent. Recently, one of us (Rivers) [10] reviewed a series of fifty-one surgically verified cases of duodenitis, gastritis and gastrojejunitis. It was suggested from this study that these shallow mucosal or submucosal lesions can be equal in importance with ulcer. A clear-cut syndrome characteristic of duodenitis could not be formulated. In a general way, the histories suggest ulcer, but in more than 50 per cent of the cases there is a liberal admixture of symptoms suggesting cholecystitis. Usually there is nausea, flatulence and vomiting, and frequently there is distress in the upper right quadrant, suggestive of a pathologic condition of the gallbladder. In cases 15 and 16, the history is that usually associated with cholecystitis, yet at operation evidence of this complication was not demonstrable. In cases 17, 18 and 19, both ulcer and duodenitis were found. In case 17, multiple ulcers and extensive duodenitis coexisted. In this case, the history includes some characteristics of ulcer; yet it is atypical since there was much complaint of nausea, dizziness and anorexia. In cases 18 and 19 there were the characteristics usually attributed to peptic ulcer.

Case 20.—A man, aged 54, gave a history of dyspepsia with characteristics of ulcer of ten years' duration. He had had pain in the epigastrium two or three hours after meals, and frequently he had had pain at night which was relieved as a rule by food. Sodium bicarbonate gave relief. For the period just before he came to the clinic he had belched a great deal. After a test meal, total acidity of the gastric contents was 50 and free hydrochloric acid, 30; the total quantity of gastric contents recovered was 340 cc. Roentgen examination disclosed an operable lesion at the pylorus. A diagnosis of pyloric lesion, probably duodenal ulcer, was made. At operation, marked thickening of the pylorus was found. About 2 cm. above this there was the crater of an ulcer. By microscopic examination, marked gastritis about the pylorus was demonstrable.

Case 21.—A woman, aged 47, for two years had had periodic attacks of nervousness and dyspepsia with much gas and nausea and some heartburn. These symptoms were somewhat worse after sausage and fried food had been eaten. On gastric analysis, total acidity was 40 and free hydrochloric acid, 26; the total quantity of gastric contents was 200 cc. Roentgen examination disclosed a small ulcer on the lesser curvature near the pylorus. At operation, gastric ulcer was found. An excised portion of the stomach had the characteristics of chronic inflammatory tissue (gastritis?).

10. Rivers, A. B.: A Consideration of Certain Etiologic Factors and Clinical Manifestations of Inflammatory Lesions of the Stomach Over Duodenum, unpublished data.

In case 20, the history is characteristic of ulcer, and it covers a period of ten years. The recent development of some pyloric obstruction probably was responsible for the belching and bloating which became troublesome several months before operation. The obstruction in this instance was due to the inflammatory process extending to the pylorus and producing pyloritis. The roentgen appearance of the lesion had some characteristics of a malignant condition. In case 21, the history has more of the characteristics usually attributed to ulcer. The roentgen disclosure of a niche near the pylorus influenced the clinician in advising surgical measures. The symptoms of gastritis are extremely indefinite; nausea, vomiting, belching and aggravation of symptoms by certain types of food are the more frequent complaints. Pain usually is not severe. In our series, operation usually was advised because roentgen examination revealed deformities suggesting gastric ulcer or carcinoma.

In 0.37 per cent of patients operated on for peptic ulcer, a diverticulum of the small intestine also was found. Meckel's diverticulum was discovered twice, and on two occasions the diverticulum was found in the duodenum. In all of these cases, a preoperative diagnosis of duodenal ulcer had been made.

Case 22.—A man, aged 41, entered the clinic because of periodic attacks of cramping epigastric pains associated with nausea and vomiting. He had been troubled in this way for twenty years. Attacks usually had continued for five or six days. At times, the pain had been severe. Occasionally he had had pain also in the lower right quadrant of the abdomen. Gastric analysis disclosed total acidity of 102 and free hydrochloric acid, 82; the total quantity of gastric contents recovered was 100 cc. A duodenal ulcer was found on roentgen examination. At operation, perforating duodenal ulcer and chronic appendicitis were found. In the ileum, about 183 cm. from the ileocecal valve, there was a Meckel's diverticulum.

Case 23.—A man, aged 35, had suffered from intervals of distress in the upper portion of the abdomen for seven years. He had had pain in the epigastrium and upper right quadrant which had waked him at night or which had come on from three to four hours after meals. There had been some belching, bloating and vomiting, which sodium bicarbonate or food usually relieved. He had been getting progressively worse for six months with more pain and shorter intervals of relief from symptoms. After a test meal, total acidity was 40 and free hydrochloric acid, 26; the total quantity of gastric contents was 180 cc. Roentgen examination revealed duodenal ulcer. At operation, subacute duodenal ulcer, chronic appendicitis and a Meckel's diverticulum were found.

In case 22, the diverticulum was found about 183 cm. from the ileocecal valve. It is unusual to find a Meckel's diverticulum further than 91.4 cm. from the ileocecal juncture. In all probability, the diverticulum in the cases cited in this paper had nothing to do with the symptoms. Occasionally a Meckel's diverticulum causes serious complications; acute inflammation with perforation may result; intussusception may originate in a Meckel's diverticulum, and occasionally it may cause

intestinal obstruction by kinking the bowel. After studying a series of such cases, Balfour [11] stated:

Meckel's diverticulum and its associated conditions should be borne in mind in obscure inflammatory processes of the lower abdomen; and especially in those cases of supposed acute appendicitis in which the appendix does not appear to be sufficiently involved to explain the symptoms, the ileum should be explored for a possibly acutely inflamed Meckel's diverticulum.

CASE 24.—A man, aged 48, gave a history that dated back twenty-seven years. The symptoms were characteristic of peptic ulcer. The pain was referred through to the back. Symptoms were worse after eating acid food or fats. Estimation of gastric acidity disclosed hyperchlorhydria. A duodenal deformity was noted by the roentgenologist. At operation, two duodenal ulcers and a duodenal diverticulum were found; the lower side of the diverticulum was attached to the pylorus. Chronic appendicitis also was found.

CASE 25.—A man, aged 45, for about nineteen years had had intervals of dyspepsia two or three hours after meals and there had been burning pain in the epigastrium, which was promptly relieved by the taking of food or sodium bicarbonate. Frequently he had been awakened at night by pain in the epigastrium. Brief periods of dieting had given relief for prolonged periods. There had been much belching and bloating during the attacks of pain. Gastric analysis revealed total acidity of 54 and free hydrochloric acid, 40; the total quantity of gastric contents was 50 cc. A duodenal ulcer was disclosed at roentgen examination. Lesions found at operation were as follows: duodenal ulcer with considerable contraction, dilation of the stomach, chronic appendicitis and a diverticulum 2 cm. long on the inferior margin of the duodenum.

The duodenal diverticula discovered in these cases probably in no way influenced the symptoms, which were quite characteristic of ulcer in both cases. We know of no syndrome or complaint regularly attributable to the presence of diverticula which would aid in diagnosing this condition. Duodenal diverticula usually can be divided into two types, developmental and acquired. Diverticula of the developmental type probably form at weak points in the bowel. They are situated within a radius of 3 cm. of the ampulla of Vater and usually are found incidentally at necropsy. In a series of cases reviewed at the clinic, apparently none of the developmental diverticula gave rise to symptoms. Nagel [12] studied nineteen cases of acquired duodenal diverticula. These were all in the first portion of the duodenum.

Three were found associated with gallbladder disease, in two of which the diverticulum appeared to have formed as a result of closure of a fistulous tract between the two organs. In one of the patients, gallstones were present in the diverticulum. Two diverticula were in patients operated on for chronic appen-

11. Balfour, D. C.: Meckel's Diverticulum: A Report of Fifteen Cases, Journal-Lancet **31**:110, 1911.

12. Nagel, G. W.: Unusual Conditions in the Duodenum and their Significance. Membranous Obstruction of the Lumen, Diverticula and Carcinoma, Arch. Surg. **11**:529 (Oct.) 1925.

dicitis and in whom the traction of adhesions around the duodenum were probably the factors producing the diverticula. The fourteen remaining were definitely associated with duodenal ulcer. The majority form just beyond the pylorus in the antero-inferior portion of the duodenum. All coats of the bowel are included in their walls and they are not due to a perforation of the base of an ulcer and resulting formation of a false pouch, but are formed by the contraction of scar tissue and pressure from within the bowel.

As miscellaneous cases, we have included one each of Lane's kink, splenitis and calcareous lymph node of the jejunum. These complications were found during laparotomy for gastric ulcer.

CASE 26.—A man, aged 39, entered the clinic because of chronic constipation. Occasionally there was nausea shortly after eating. There was an uncomfortable sensation of fulness in the upper part of the abdomen but no pain. The symptoms were mild and did not incapacitate the patient for his work. Gastric analysis disclosed total acidity of 40 and free hydrochloric acid of 20; 180 cc. of gastric contents were recovered. A gastric ulcer, with some retention, was recognized at roentgen examination. At operation, in addition to gastric ulcer and chronic appendicitis, a Lane's kink was found.

There is no information in this history which would lead one to suspect that this patient might have gastric ulcer, chronic appendicitis and Lane's kink. In fact, all the complaints easily could have been caused by the chronic constipation. It might be assumed that the Lane's kink, a developmental condition resulting from fixation by bands of the terminal 91 cm. of the ileum, was responsible for the symptoms.

For several years, considerable importance was attached to the presence of Lane's kink in the ileum. Various operations were devised and performed to liberate or circumvent the alleged obstruction caused by this condition, and although a few patients probably were improved in condition, many more were no better, and not a few were decidedly worse after such surgical procedures.

CASE 27.—A woman, aged 40, gave a history of intermittent stomach trouble of seven years' duration. At intervals, the pain had become sharp, had been referred from the epigastrium to the back and occasionally had extended upward to the left shoulder. The distress usually had come on about an hour after meals, and the taking of more food had relieved it temporarily. She had been comfortable on a milk diet. Migraine and constipation had been associated with the other symptoms. She had lost 18.1 Kg. in four years. Gastric analysis revealed total acidity of 40 and free hydrochloric acid, 32; 160 cc. of gastric contents were recovered. Results of a roentgen examination were negative. A diagnosis of peptic ulcer was made. At operation a gastric ulcer and chronic appendicitis were found. A degenerating calcareous lymph node was removed from the mesentery of the jejunum.

The history in this case presents the usual characteristics of ulcer. The degenerating calcareous lymph node which was found on the jejunal mesentery is not of particular clinical significance.

CASE 28.—A man, aged 43, began having dyspepsia eighteen years prior to his examination at the clinic. He described intermittent pain situated about the umbilicus, coming on two or three hours after eating. Food relieved the pain. Early in the history he had had gastric hemorrhages on two occasions. The symptoms, after persisting for ten months, had disappeared, and the patient had remained well for fifteen years. Three years, and again one year, before coming to the clinic he had had a brief period of recurrent trouble. During the two months prior to his visit to the clinic, he had had daily pain in the epigastrium, which had come on two or three hours after eating and which had been relieved by taking sodium bicarbonate. He had been markedly constipated. Roentgen examination revealed gastric and duodenal deformities. Estimation of gastric acidity disclosed slight hyperchlorhydria. At operation perforated gastric ulcer, chronic duodenal ulcer, chronic pancreatitis, chronic splenitis and chronic appendicitis were found. Partial gastrectomy, splenectomy and appendectomy were performed. Convalescence was uneventful.

The history in this case was characteristic of ulcer and included hemorrhages. Whenever the operating surgeon is not entirely certain that bleeding comes from a definitely active ulcer, a thorough search for extragastric causes for it is obligatory. In this case, splenitis was discovered and the spleen was removed, thus possibly avoiding a subsequent operation. The spleen may be instrumental in several ways in the production of gastro-intestinal hemorrhage: (1) in a mechanical way, by causing venous engorgement of the mucous membrane of the stomach secondary to thrombophlebitis of the splenic veins, and (2) by serving as a focus in activating hepatic cirrhosis, which in turn, of course, is a frequent cause of bleeding from the stomach.

In going over the records of the 1,075 cases included in this series, it may be noted that seven patients with a preoperative diagnosis of duodenal ulcer were found at operation to have ulcers only in the stomach.

CASE 29.—A man, aged 39, gave a good history of ulcer of three years' duration. He complained of pain in the epigastrium and in the upper left quadrant and reported relief from the taking of food and sodium bicarbonate. Shortly before he came to the clinic he had vomited large amounts of watery material. After a test meal, total acidity was 84 and free hydrochloric acid, 60; the total quantity of gastric contents recovered was 130 cc. Results of roentgen examination of the stomach were negative. A diagnosis of duodenal ulcer was ventured. At operation, chronic appendicitis and a chronic gastric ulcer, 5 cm. above the pylorus, were found.

CASE 30.—A man, aged 36, gave a history of having had, for seven years, dyspepsia of a type suggestive of ulcer. This included epigastric pain which came on one and a half to two hours after meals, and which radiated through to the back. Taking of food and of sodium bicarbonate relieved this pain. He had had some pain at night. Inadequate relief had been obtained from the type of diet employed for ulcer. Gastric analysis revealed total acidity of 80 and free hydrochloric acid of 60; the total quantity of gastric contents recovered was 300 cc. The gastric contents contained undigested remnants of food. Diagnosis by roentgen methods was indeterminate. A diagnosis of duodenal ulcer was made.

At operation, a gastric ulcer and chronic appendicitis were found. The ulcer was situated on the lesser curvature about one third of the way from the pylorus to the cardia.

CASE 31.—A man, aged 55, complained of distress which was characteristic of ulcer and which had troubled him over a period of six years. At first, there had been prolonged periods of freedom from symptoms, but later the distress had occurred daily. During the year prior to examination at the clinic, he had had much flatulence but no vomiting. After a test meal, the total acidity was 80 and the free hydrochloric acid, 60; 250 cc. of gastric contents were recovered. Roentgenographically, a lesion was evident in the pyloric ring. A diagnosis was made of pyloric obstruction, probably caused by duodenal ulcer. At operation, a subacute gastric ulcer was found 3 cm. above the pylorus. Microscopic study of the tissue showed a simple gastric ulcer.

CASE 32.—A man, aged 55, had had dyspepsia for fourteen years. In the history were the usual characteristics of ulcer: at first, prolonged periods of freedom from distress; more recently, almost daily trouble. The pain never had been very severe, and food usually had relieved him temporarily. A perforated duodenal ulcer was found at roentgen examination. At operation, a perforating gastric ulcer was found near the pylorus; it did not appear to be malignant.

CASE 33.—A man, aged 56, had had dyspepsia for nine years. Nausea had come on two hours after eating. More recently he had had much gas and bloating one and a half hours after meals, and occasionally he had vomited. He had obtained relief after taking food or sodium bicarbonate. He had not suffered much pain. After a test meal there was total acidity of 70 and free hydrochloric acid of 52; 120 cc. of gastric contents were recovered. A duodenal deformity was evident on roentgen examination. At operation, a gastric ulcer was found 3 cm. from the pylorus; the stomach was dilated; hepatitis and chronic appendicitis also were found; the gallbladder was normal.

CASE 34.—A man, aged 42, had had dyspepsia at intervals for eight years. Epigastric pain usually had come on two hours after meals although it might occur while he was eating. Sodium bicarbonate had no effect on it. When pain was at its maximum, he had become nauseated and at times had vomited. After a test meal, total acidity was 76 and free hydrochloric acid, 60; 305 cc. of gastric contents were recovered. Roentgen examination disclosed duodenal deformity. At operation, the patient was found to have subacute appendicitis and a gastric ulcer in the median portion of the lesser curvature.

CASE 35.—A woman, aged 52, had had dyspepsia for two years with anorexia, nausea shortly after meals, vomiting and constipation. There had been no pain. After a test meal, total acidity was 60 and free hydrochloric acid, 42; 350 cc. of gastric contents were recovered. A duodenal deformity was found on roentgen examination. At operation gastric ulcer was found, with much inflammation extending to the pylorus and duodenum.

In these cases, 29 to 35, there were definite characteristics of ulcer in the history. In case 29 a deformity was not found by roentgen examination in either the stomach or duodenum. In case 30, the roentgen diagnosis was indeterminate. These histories were characteristic of ulcer, and the estimation of gastric acidity revealed hyperchlorhydria. From the data available, the clinician was not justified in making a more specific diagnosis than peptic ulcer. In case 31, the diagnosis of

carcinoma was not excluded. It has been pointed out by many observers that it is impossible from the history alone to differentiate gastric and duodenal ulcer. The clinician, in these instances, probably was influenced in making the diagnosis of duodenal ulcer for no other reason than that by surgical methods it has been proved to be far more common than gastric ulcer. In cases 31, 33 and 34, the histories were excellent examples of those found when peptic lesions are present, and the roentgenologists made diagnoses of duodenal ulcer. This should have been sufficient evidence to warrant the clinicians' diagnosis of duodenal ulcer. Carman,[13] in discussing the accuracy of roentgen diagnosis, stated that in a series reviewed by him roentgen diagnosis was correct in cases of peptic ulcer in 98.21 per cent, whereas in the localization of ulcer it was correct in more than 95 per cent.

It is difficult to distinguish any feature suggesting peptic ulcer, clinically, in case 35. In view of the extensive inflammatory reaction involving the pylorus and duodenum, it is not difficult to understand why a roentgenologic error was made in this case. In a paper dealing with the limitations of roentgenologic diagnosis, Carman[14] wrote: "Lesions near the pylorus are often lacking in differential signs and it may be impossible to determine whether the distortion of the pyloric region is due to a small carcinoma, a gastric ulcer, a duodenal ulcer with extensive adhesions or a syphilitic lesion."

The errors in diagnosis illustrated in this group are not of any great significance. These cases were analyzed separately because we wanted to know not only what the operative data were when the major lesion seemed preoperatively to be either gastric or duodenal ulcer, but also whether these histories contained evidence which should have made clinicians suspect the conditions which remained undiagnosed.

SUMMARY AND CONCLUSIONS

1. The lesions found in association with ulcer when this has been considered the condition of major importance have been studied, and their relative frequency has been outlined graphically in figure 1.

2. More careful evaluation of symptoms and painstaking general examination of the patient undoubtedly would be followed by greater accuracy in diagnosis. Associated acute or subacute appendicitis should, under these conditions, be recognized much more frequently. That greater accuracy in diagnosis would benefit the patient seems hardly questionable. The better we understand all the factors influencing the

13. Carman, R. D.: The Roentgen Diagnosis and Localization of Peptic Ulcer, California State J. Med. **18**:377, 1920.

14. Carman, R. D.: Limitations of Roentgenologic Diagnosis, New York State J. Med. **22**:302, 1922.

symptoms under consideration, the more intelligently suitable measures for relief can be instituted.

3. In discussing the advisability of adopting surgical methods in the treatment of patients with peptic ulcer because of the probability of finding associated lesions of importance, one must make distinctions; for this reason, it is obligatory to consider gastric and duodenal ulcer separately.

Analysis of chart 2, which includes only those cases diagnosed as instances of duodenal ulcer, shows that in but a single instance was a malignant condition found as a complicating lesion. The patient had pyloric obstruction, obviously a complication, and for treatment surgical procedures would without question be advised.

The associated observation of chronic appendicitis should not be considered of great importance because it is extremely doubtful that the presence of this complication was in any way contributory to the symptoms from which these patients sought relief.

The finding of acute or subacute appendicitis is undoubtedly of definite importance. That occasionally acute appendicitis may be masked by complicating ulcer, so that its presence will remain unsuspected, seems possible. It seems, however, that this complication usually would present features sufficiently definite to be indicative of its presence and that failure to find it is likely to be due to remiss methods of diagnosis or inattention to details by the examining clinician or surgeon.

Rare complications, such as gastric ulcer associated with diverticula in the ileum or duodenum and with benign tumors, are not of paramount importance; and it would seem, therefore, that one is hardly justified in allowing the probability of finding important associated disease to exert any influence in deciding on the advisability of adopting surgical measures for ulcers, when otherwise a medical regimen might be the treatment of choice.

With gastric ulcers, however, the probability of finding serious complications is a little greater. There is always the disquieting possibility that the ulcer under consideration is malignant. In 2.1 per cent of these cases, the surgeon found lesions with some characteristics of malignancy. Since there was no preoperative suggestion by clinicians that the lesion might be malignant, this seems of greater significance than otherwise. In about 50 per cent of the histories in this group one can find evidence which should have made the clinician suspicious of carcinoma. In some cases, the surgeon's assumption that a malignant condition was present probably was made on insufficient evidence, because a few of these patients are living and apparently are in good health despite the fact that the lesions were not removed at the time of the operation.

The fact remains, however, that we do not have criteria which can be relied on to reassure us that any gastric ulcer is not potentially

malignant. This fact cannot be ignored when the advisability of various types of treatment for gastric ulcer is under consideration.

4. Consideration of rare complications of peptic ulcer which were not diagnosed preoperatively disclosed five cases complicated by duodenitis or gastritis; two by Meckel's diverticulum; two by duodenal diverticulum, and one each by Lane's kink, splenitis, calcareous lymph node of the jejunum, pancreatic cyst, fibroma of the jejunum and cyst of the suspensory ligament of the liver. In seven instances, in which duodenal ulcer was diagnosed, gastric ulcers only were found at operation. Great significance should not be attached to the finding of most of these lesions. There was no pathologic feature of great importance in this entire group except for the cases of splenitis and pancreatic cyst. It seems unlikely that the most careful evaluation of symptoms and objective observations would have sufficed to make an accurate diagnosis in most of these cases.

5. When at least the more frequent of the lesions associated with peptic ulcer are borne in mind, the probability of accurate diagnosis should be increased. This added efficiency would make the clinician increasingly authoritative in his opinions regarding the advisability of various therapeutic procedures.

THE PITUITARY GLAND AND THE SUPRARENAL CORTEX *

ROBERT C. MOEHLIG, M.D.
DETROIT

The pituitary gland is functionally related to the suprarenal cortex, and this relationship can be understood from embryologic considerations. There can be no question but that glandular interrelationships have made it difficult to understand many problems in endocrinology. As Hoskins [1] has shown, there are almost innumerable combinations possible between the endocrine glands. It is, therefore, with some hesitancy that a discussion is undertaken to point out a particular correlation. The explanation to be offered finds its strength in its agreement with the known clinical, pathologic and experimental facts, and is based on sound fundamentals of embryology.

Aplastic states of the pituitary gland are concomitant with aplasia of the suprarenal cortex and, conversely, hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex.

From the clinical side, the best examples of the aplastic and deformed pituitary are found in anencephalic fetuses. Hemicephaly, oxycephaly and other developmental defects are accompanied at times by developmental defects of the pituitary gland.

Ballantyne [2] described forty-five anencephalic fetuses and stated that the pituitary gland rarely was present. Schwalbe,[2] Haberfeld [2] and Wrete,[2] on the other hand, found that the pituitary gland was present.

Mauksch [3] found that the gland was present but abnormal; in some cases it consisted of only two lobes. Browne [4] found no trace of a pituitary gland in five anencephalic fetuses. Covell [5] studied thirty-two anencephalic fetuses and concluded that: the pituitary is extremely variable in weight, being less than normal; the pars nervosa is lacking in the majority of cases; the pars intermedia is variable as to both occurrence

* Submitted for publication, March 10, 1929.

* From the Department of Internal Medicine, Harper Hospital, Detroit.

1. Hoskins, R. G.: Recent Work on Internal Secretions, Endocrinology **6**:621 (Sept.) 1922.

2. Cited by Covell (footnote 5).

3. Mauksch: Das Verhalten der Hypophyse und des Canalis Craniopharyngeus in neun Fallen von Kranioschisis untersucht, Anat. Anz. **54**:248, 1921.

4. Browne, F. J.: The Anencephalic Syndrome in Its Relation to Apituitarism, Edinburgh M. J. **25**:296, 1920.

5. Covell, W. P.: Quantitative Study of Hypophysis of Human Anencephalic Fetus, Am. J. Path. **3**:17 (Jan.) 1927.

and volume. Kraus [6] found that the most frequent developmental anomalies of the pituitary gland are seen in anencephalus, with the posterior lobe frequently absent. Barlow [7] also found apituitarism in anencephalic fetuses. Kiyono,[8] studying the pathologic anatomy of the endocrine glands in anencephalus, found striking pituitary defects. Pituitary defects are, therefore, a frequent observation in anencephalus.

It has long been known that aplastic states of the suprarenal cortex accompany cerebral defects, such as anencephalus and acrania, as well as some forms of hydrocephalus. Several authors hold the opinion that the defect of the suprarenal cortex is responsible for defect of the brain (Alexander [9]), whereas others believe that the cerebral defect is responsible for the suprarenal condition (Weigert,[9] Kern,[9] Myers,[9] Landau,[9] Kohn,[9] etc.). Myers [9] has disproved the theory that the suprarenal cortex is responsible for the cerebral defect. He showed that there is no developmental defect of the suprarenal cortex in anencephalic fetuses before the fifth month.

Among older writers, Zander [10] and Weigert [9] made the singular observation that the suprarenal cortex is aplastic only when the anterior portion of the brain is involved in anencephalus. One may accept the statement from the present knowledge of the facts that the anterior cerebral defects have involved the pituitary gland through its anatomic location.

In all these cases of cerebral defect only the suprarenal cortex is involved, whereas the medullary portion of the suprarenal is normal.

In some cases (Landau [9]), the suprarenal cortex was entirely missing. According to Dietrich and Siegmund,[11] there is no regular parallelism between the degree of the cerebral defect and that of the defect of the suprarenal cortex, and there is no clear explanation. Certainly, one must modify one's views to the opinion that the degree of defect of the suprarenal cortex is dependent on the degree of involvement of the pituitary gland and not related to the cerebral defect per se.

Kohn [12] has recently taken the view that the pituitary gland is the responsible factor for the defect of the suprarenal cortex. From his

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6. Kraus, E. J.: In Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 810.

7. Barlow, D. L.: Apituitarism and the Anencephalic Syndrome, Brit. M. J. **1**:15, 1923.

8. Kiyono: Pathologische Anatomie der endokrine Organen bei Anenzephalie, Virchows Arch. f. path. Anat. **257**:441, 1925.

9. Cited by Dietrich and Siegmund (footnote 11).

10. Zander, R.: Ueber functionelle und kinetische Beziehungen der Nebennieren zu anderen Organen, speziell zum Grosshirn, Beitr. z. Physiol. **7**:489, 1890.

11. Dietrich, R., and Siegmund, J., in Handbuch der speziellen pathologischen Anatomie und Histologie, 1926, p. 951.

12. Kohn, A.: Anenzephalie und der Nebennieren, Arch. f. Entwcklngsmechn. d. Organ. **102**:113, 1924.

histologic studies of anencephalic fetuses, he noted that the epithelial portion of the pituitary gland was involved, there being scarcity of oxyphil and large basophil cells. Defects were noted in the infundibulum and pars nervosa. He based his opinion concerning the relationship of the pituitary gland and the suprarenal cortex on the well known clinical examples of pituitary atrophy (such as seen in pituitary dwarfism) with concomitant atrophy of the suprarenal cortex. He, therefore, placed the primary responsibility on the pituitary gland.

Further clinical proof of this relationship is furnished by cases of hypopituitarism, such as dystrophia adiposogenitalis, in which the pituitary disturbance is accompanied by various degrees of atrophy and aplasia of the suprarenal cortex. Postmortem studies of these cases have shown atrophy of the suprarenal cortex (Falta,[13] Kraus,[6] and others). Dietrich and Siegmund [11] called attention to the well known association of atrophy of the pituitary gland and of the suprarenal cortex.

Experimental proof of the rôle of the pituitary gland in atrophy of the suprarenal cortex has also been provided. Smith,[14] by hypophysectomy in the rat, produced a hypoplasia of the suprarenal cortex. The cortex is sensibly reduced in volume. The medulla is slightly if any altered. Landau [9] found the suprarenal cortex to be of this type in anencephalus.

Askoli and Legnani [15] found hemorrhages in the suprarenal cortex and an altered fat content after hypophyseal extirpation experiments.

Reichert [16] reported that the suprarenal glands of his puppies on which hypophysectomy had been performed were smaller than those of the controls.

The reverse picture has also been demonstrated. Falta,[13] in defining acromegaly, says (in italics) that one finds apparently "frequently hyperplasia of the suprarenal cortex." Fischer [17] found enormous suprarenal glands, the enlargement especially affecting the cortex. Fischer and Schultze [18] found enlargement of the suprarenal glands in two cases of acromegaly, in one of which the glands were at least five times the

13. Falta, William: The Ductless Glandular Diseases, Philadelphia, P. Blakiston's Son & Company, ed. 2, 1916, p. 235.

14. Smith, P. E.: Disabilities Caused by Hypophysectomy and Their Repair; Tuberal (Hypothalmic) Syndrome in Rat, J. A. M. A. **88**:158 (Jan. 15) 1927.

15. Askoli and Legnani, cited by Kraus (footnote 6).

16. Reichert, F.: The Results of Replacement Therapy in an Hypophysectomized Puppy, **12**:451 (July-Aug.) 1928.

17. Fischer, B.: Hypophyse und Akromegalie, Frankfurt. Ztschr. f. Path. **11**:130, 1912.

18. Fischer, B., and Schultze, F.: Zur Lehre von der Akromegalie und Osteoarthopathie hypertrophiantiante, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **24**:607, 1912.

normal size. Bassoe [19] said that the suprarenal glands have often been found enlarged at necropsy. He quoted Amsler, Ausch, Eltester and Schroeder, Mullaly, Horbitz and others as saying that large suprarenal glands are found in acromegaly.

It has been shown that acromegaly is associated at times with tumors of the suprarenal cortex.

According to Kraus,[6] the hypertrophy of the suprarenal glands is due to hyperplasia of the pituitary eosinophil cells, whereas hypoplasia of these cells produces atrophy of the suprarenal glands.

Hofstätter [20] was able to produce hypertrophy of the suprarenal cortex by injections of posterior lobe extract. He used rabbits for his experiments, and the changes were noticeable around the thirtieth day.

In analyzing the data submitted, one is forced to the conclusion that pituitary disturbances affect the suprarenal cortex and not the suprarenal medulla.

The explanation of these correlations can be found in an analysis of the embryologic relationships. I [21] have shown elsewhere that the pituitary gland has a selective action on mesenchymal tissues.

Attention is called to the fact that the suprarenal cortex is a mesenchymal tissue in contrast to the suprarenal medulla, which is an ectodermal tissue.[1]

Some of the relationships between the pituitary and mesenchymal tissues are obvious and need not be discussed. No emphasis is needed, for instance, to show the relationship of the pituitary gland to bone and cartilage. Its relationship to fat metabolism is also undisputed and while its exact modus operandi is still unknown, nevertheless it has a definite place in fat metabolism. It is a natural sequence of thought that, if the suprarenal cortex reflects the state of the pituitary gland, the cholesterol metabolism would be involved. A discussion of this relationship must be left for the future, but the importance is obvious.

The selective action of the posterior pituitary extract when injected hypodermically is exerted on three mesenchymal tissues; it produces a contraction of the blood vessels, contraction of smooth muscle, such as that of the bladder and intestine, and a varying effect (diuresis or anti-

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19. Bassoe, P.: Acromegaly, Endocrinology and Metabolism, New York, D. Appleton & Company, 1922, vol. 1, p. 809.

20. Hofstätter, R.: Ueber Befunde bei hyperhypophysierten Tieren, Monatschr. f. Gebürtsh. u. Gynäk. 49:387, 1919.

21. Moehlig, R.: Embryohormonic Relations of Pituitary Gland to Mesenchymal Tissues, Ann. Int. Med. **1**:563 (Feb.) 1928; Embryohormonic Relations of the Suprarenal Cortex to Mesothelial Tissues, ibid. **1**:563, 1928; Selective Action of the Suprarenal Cortex Secretion on Mesothelial Tissues, Am. J. M. Sc. **168**:553, 1924. Moehlig, R., and Ainslee, H. B.: Pituitary Gland and Cholesterol Metabolism, Ann. Clin. Med. **5**:772, 1927.

diuresis) on the renal cells. Other articles [21] have gone into more detailed discussion concerning this selective action.

It was also shown that the suprarenal cortex has a selective action on a specialized part of the mesoderm, the mesothelium from which the sex glands and skeletal musculature are derived. On the basis that with involvement of the pituitary gland there is a concomitant involvement of the suprarenal cortex, these mesothelial tissues must also be considered to share in the symptomatology and pathology. This is, of course, a well known clinical fact, illustrated by many clinical examples, such as dystrophia adiposogenitalis with the involvement of the sex gland and muscular fatigue. In the anencephalic fetuses with pituitary anomalies, one should see the symptoms of apituitarism with the involvement of the mesenchymal tissue. The *British Medical Journal*,[22] in a comment on Browne's work with anencephalic fetuses, states that the most rigorous search on the basis cranii of his anencephalic fetuses revealed absolutely no trace of a pituitary gland. The syndrome with obesity, hypoplasia of the suprarenal glands and genital organs and stunted growth of body and limbs, agrees in the main with features of the condition called apituitarism.

It is to be noted that the embryohormonic relations of the pituitary to mesenchymal tissues, will explain the involvement of the suprarenal cortex.

SUMMARY

Anencephalus is accompanied by pituitary anomalies. The degree of anomaly varies in different cases, being greatest in anterior cerebral defects. The suprarenal cortex reflects the state of the pituitary gland and is always hypoplastic when the pituitary is involved in anencephalus. Hyperplasia of the pituitary gland results in hyperplasia of the suprarenal cortex.

The view that cerebral defects are responsible for aplasia of the suprarenal cortex must be modified to the view that the pituitary gland is the responsible factor.

It is to be emphasized that only the suprarenal cortex and not the medulla is involved in these pituitary anomalies, and the same holds true for experimental hypophysectomy.

The embryohormonic relation of the pituitary to mesenchymal tissues gives a clearcut explanation of this singular involvement.

The importance of the relation of the pituitary gland to the suprarenal cortex is readily realized when cholesterol metabolism is considered. Many related problems can be studied with a newer and better foundation.

22. Editorial, Brit. M. J. **2**:828, 1920.

THE EFFECT OF UNCOOKED STARCHES ON THE BLOOD SUGAR OF NORMAL AND OF DIABETIC SUBJECTS. II.*

SANFORD M. ROSENTHAL, M.D.
AND
EDWIN E. ZIEGLER, M.D.
WASHINGTON, D. C.

In previous work,[1] raw starch was administered by mouth to rabbits as a means of studying pancreatic function and upper intestinal digestion. In these animals, a rise in blood sugar was uniformly produced; the average rise in the rabbits amounted to 62 mg. per hundred cubic centimeters. This elevation of blood sugar is dependent on the liberation of dextrose from the starch molecule, and the hyperglycemia was shown to afford a means of estimating the activity of pancreatic diastase, on the one hand, and under conditions in which diastatic ferments are normally present, a means of studying other factors which influence the rate of digestion of starch in the alimentary canal.

The Effect of 2 Gm. of Raw Starch Per Kilogram of Body Weight on the Blood Sugar of Normal Dogs (Administered by Stomach Tube in 200 Cc. of Water)

	Blood Sugar, Mg. per 100 Cc.			
	Before	After One-Half Hour	After One Hour	After Three Hours
Dog, 15 Kg., 30 Gm. raw starch	0.097 0.105	0.185 0.140	0.131 0.150	0.121 0.117
Dog, 11.4 Kg., 23 Gm. Starch	0.089	0.138	0.148	0.115

Approximately 5 Gm. of starch per kilogram of body weight was used in rabbits. Three tests were performed on dogs to which 2 Gm. of starch per kilogram of body weight was given. With this quantity, rises in blood sugar occurred which were comparable to those obtained in rabbits, as shown in the accompanying table.

Several workers [2] have employed cooked starch to obtain sugar tolerance curves in human subjects, and Maclean found that 50 Gm. of

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* From George Washington University Hospital and the Hygienic Laboratory.

1. Rosenthal, S. M.: Pancreatic Function and Upper Intestinal Digestion, Arch. Int. Med. **41**:867 (June) 1928.

2. Maclean, H.: Glycosuria and Diabetes, London, Constable & Co., 1924. Gray, H.: Blood Sugar Standards, Arch. Int. Med. **31**:241 (Feb.) 1923. Rowe, A. H., and Rogers, H.: Carbohydrate Tolerance in Normal Persons and in Nondiabetic Patients, Arch. Int. Med. **39**:330 (March) 1927.

cooked oatmeal, rice or potatoes would produce a rise in blood sugar comparable to 50 Gm. of dextrose. However, when we gave from 50 to 75 Gm. of raw starch to a group of patients, there was a striking absence of increase in blood sugar.

METHOD AND RESULTS

Soluble starch prepared according to Lintner was used. It was stirred into 250 cc. of water, and 2 cc. of normal (3.6 per cent) hydrochloric acid was added just before it was given. The acid makes the mixture more palatable and on theoretical considerations would prevent any digestion of the starch by the saliva. However, previous work on rabbits and further work on human beings indicate that no appreciable salivary digestion of uncooked starch takes place, for the effects on blood sugar were the same when acid was omitted as when it was employed. It will be interesting to know whether salivary digestion takes place to a greater extent in cases of gastric anacidity.

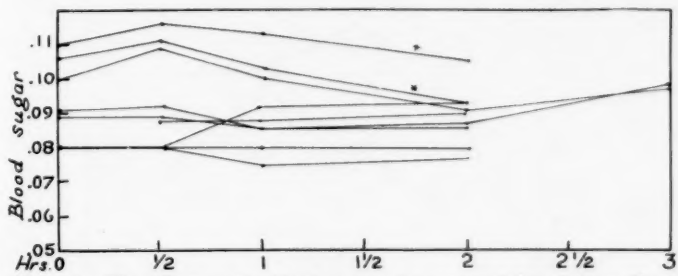

Chart 1.—The effect on the blood sugar of normal adults of from 50 to 75 Gm. of raw starch administered by mouth in 250 cc. of water plus 2 cc. of normal hydrochloric acid. The curves marked * represent 75 Gm. doses.

Fifty grams of starch was administered to seven, and 75 Gm. to two, hospital patients free from alimentary disease or diabetes. The results are shown in chart 1. The blood sugar showed an average increase of 1 mg. per hundred cubic centimeters in one-half hour, a decrease of 1.2 mg. in one hour and a decrease of 3 mg. in two hours. These results present a striking difference from those obtained in a group of twelve patients to whom 50 Gm. of cooked starch was given in the form of mashed potatoes (250 Gm.) made up to 500 cc. in water, and to which from 6 to 10 cc. of 3.6 per cent hydrochloric acid was added. The experiments with cooked starches will be reported in detail elsewhere, as a technical procedure for studying pancreatic function and intestinal digestion in human subjects. An average increase of 56 mg. occurred in one-half hour, of 51 mg. in one hour and of 11 mg. per hundred cubic centimeters in two hours after the test meal (chart 2).

Another series of tests were performed on seven diabetic patients to whom no insulin had been given for several days preceding the experiments. The results are shown in chart 3. There was an average increase in blood sugar of 6 mg. per hundred cubic centimeters in one-

half hour, a decrease of 9 mg. in one hour, and a decrease of 14 mg. in two and one-half hours after the starch meal. This fall in blood sugar below the initial value is worthy of notice, for it occurred in seven of the nine control cases and in five of the seven diabetic patients. In the normal subjects the fall was negligible, but in the diabetic patients the decrease varied from 14 to 35 mg. per hundred cubic centimeters. We do not know whether this fall would have occurred spontaneously or whether it was associated with the starch meal.

A form of carbohydrate which does not raise the blood sugar would be highly desirable in a diabetic regimen, for it would obviate the neces-

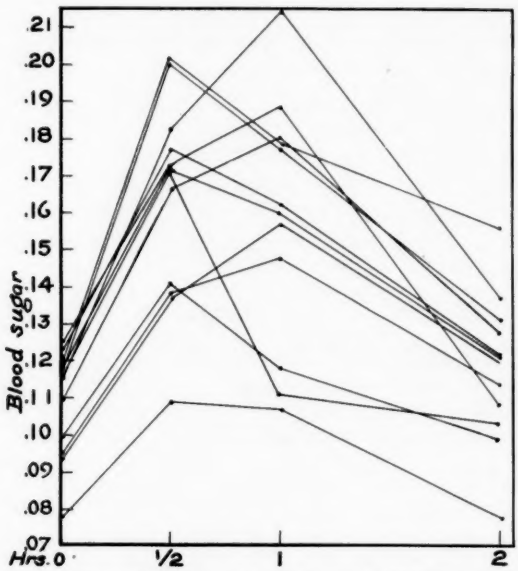

Chart 2.—The effect of 50 Gm. of cooked starch (250 Gm. of potatoes) on the blood sugar of normal adults. Administered by mouth in 500 cc. of water plus from 6 to 10 cc. of normal hydrochloric acid.

sity of insulin for those patients with moderately severe forms of the disease who develop hyperglycemia and glycosuria after large meals. Further investigation must determine to what extent tolerance can be increased by employing a maintainance diet high in raw starch.

Efforts are being made to employ those foods in which raw starch occurs in an edible form. One of us (R.) took a test breakfast of 500 Gm. of raw carrots (50 Gm. of carbohydrate). They were chewed normally without any attempt to diminish salivary action. Determinations of blood sugar showed: before the meal, 0.091 mg. per hundred

cubic centimeters; forty-five minutes after, 0.092 mg.; one and one-half hours after, 0.086 mg. and three hours after, 0.086 mg. Subsequent examination of the stools revealed no appreciable quantities of starch or dextrins. To three diabetic patients a meal of 120 Gm. of fresh grated chestnuts was given. Blood sugars during the following three hours showed no elevation. Other edible raw foods, selected because of their

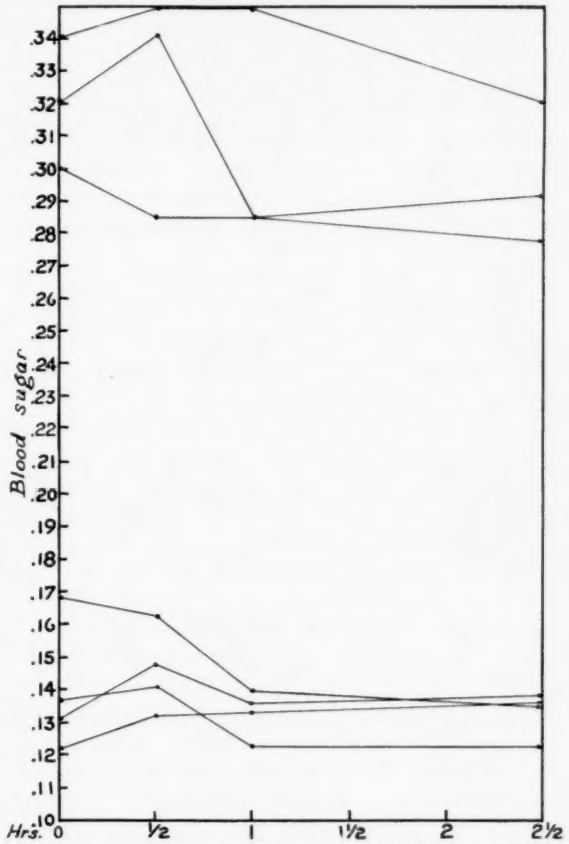

Chart 3.—Blood sugar curves following the administration of 50 Gm. of raw starch to diabetic patients. Administered by mouth in 250 cc. of water plus 2 cc. of normal hydrochloric acid.

high caloric value and because the carbohydrates are present principally in the form of starch, such as cocoanut, turnip and onion, are being studied from this point of view. Raw starch itself can be made more palatable by administering it in sweet milk or buttermilk, or in gelatin or frozen puddings.

COMMENT

In the absence of hyperglycemic effects of raw starches, the question naturally arises as to their digestibility in the alimentary canal. Langworthy [3] kept human subjects on test diets of raw starches for three day periods. The starches were given in a frozen pudding, and examinations of the stools were made to determine their digestibility. Corn, wheat, cassava, rice and taro root starch were completely digested when eaten in amounts up to 250 Gm. a day. Potato starch was digested to the extent of 97 per cent when 59 Gm. a day was given, and 78 per cent when approximately 200 Gm. a day was given. The digestion probably occurs in the distal portion of the alimentary canal, where bacterial action is an accessory to ferment action. The liberation of absorbable sugars would be sufficiently slow so that a hyperglycemia is not produced. This slow absorption does away with the sharp rise in blood sugar that normally occurs following the ingestion of other carbohydrates.

The introduction of this principle into the treatment of diabetic patients is being investigated from the point of view of obviating the use of insulin in mild and moderately severe cases, and to determine whether the total carbohydrate tolerance can be increased by this method of administration.

Another point of interest is the difference in response that occurs between the man and the other animals studied: the dog and the rabbit. It would be expected that the rabbit could rapidly digest raw starch, for this is his native diet, and the amylase in the pancreatic secretion of the rabbit is in a higher concentration than in man. The site of digestion of raw starch in man has been a subject of extensive investigation. Strasburger and his colleagues,[4] as a result of experiments in vitro, have recently concluded that digestion takes place in both the small and the large intestine. Our experiments, especially in the light of positive manifestations in animals, prove that no appreciable digestion of raw starch takes place in the upper part of the small intestine of human beings.

The starch that we used (soluble starch) has been treated with strong acid in the process of manufacture and is actually a mixture of starch and higher dextrins. With the use of untreated raw starches, either as such or in the form of uncooked vegetables or nuts, it is possible that the small increases in blood sugar (1 mg. in normal subjects and 6 mg. in diabetic patients) at the half hour period after administration will not occur.

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3. Langworthy, C. F., and Merrill, A. T.: Bull. 1213, U. S. Department of Agriculture, 1924. Langworthy, C. F., and Deuel, H. J.: J. Biol. Chem. **51**:251, 1922.

4. Strasburger, J.: Arch. f. Verdauungskr. **41**:1, 1927. Strauss: Ibid. **41**: 11, 1927. Marx, A. V.: Ibid. **41**:180, 1927. Heupke: Ibid. **41**:193, 214, 1927.

The absence of hyperglycemic effects of uncooked starches led us to question whether alimentary hyperglycemia is, in a broad sense, physiologic to man. Krasnjanskii [5] and Trimble and Maddock [6] found considerable elevations of blood sugar after each meal, and this was due solely to the carbohydrate content.

The relation of these daily rises in blood sugar to the etiology of diabetes was further suggested by an inquiry into the incidence of diabetes among the Eskimos. These people eat almost no carbohydrate. Dr. H. L. Paddon, for seventeen years in charge of a Labrador hospital

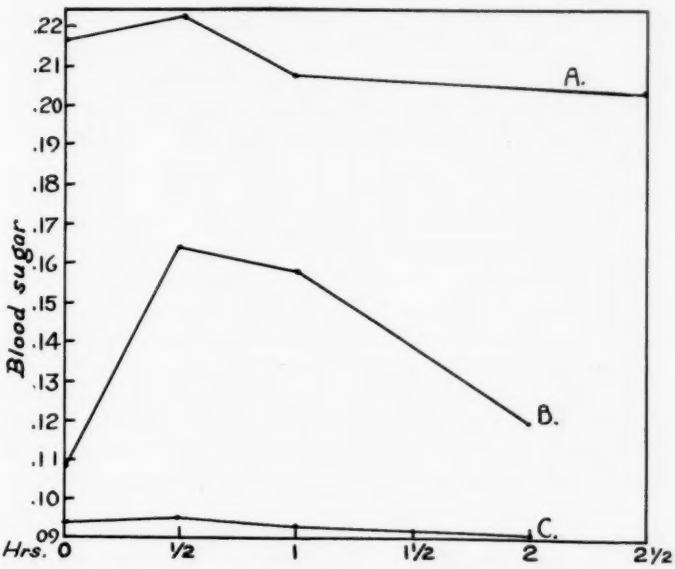

Chart 4.—Summary of blood sugar curves following the feeding of starch to human beings. *A*, 50 Gm. of raw starch to seven diabetic patients; *B*, 50 Gm. of cooked starch (250 Gm. of potatoes) to twelve normal subjects; *C*, 50 Gm. of raw starch to nine normal subjects.

as a member of Sir Wilfred Grenfell's staff, also Dr. W. A. Thomas and Captain MacMillan, have written me that they have never encountered diabetes in an Eskimo. Dr. A. Bertelson of Copenhagen wrote that a survey of the records shows that among 14,000 Greenland Eskimos who are cared for by ten Danish physicians, diabetes has never been reported to occur.

5. Krasnjanskii, L. M.: Biochem. Ztschr. **205**:180, 1929.

6. Trimble, H. C., and Maddock, S. J.: J. Biol. Chem. **81**:595, 1929.

SUMMARY

From 50 to 75 Gm. of raw starch administered by mouth to nine normal adults produced the following changes in blood sugar: in one-half hour, an average increase of 1 mg. per hundred cubic centimeters; in one hour, a decrease of 1.2 mg., and in two hours, a decrease of 3 mg.

Fifty grams of cooked starch (250 Gm. of potatoes) given to twelve persons caused the following changes in blood sugar: in one-half hour, an average increase of 56 mg.; in one hour, an increase of 51 mg., and in two hours, an increase of 11 mg.

Fifty grams of uncooked starch was given to seven patients with diabetes of varying severity; the changes in blood sugar were (average): in one-half hour, an increase of 6 mg.; in one hour, a decrease of 9 mg., and in two and one-half hours, a decrease of 14 mg.

One hundred and twenty grams of uncooked chestnuts were given to three diabetic patients without raising the blood sugar level.

THE AMINO-ACID CONTENT OF THE BLOOD IN HEALTH AND IN DISEASE *

E. G. SCHMIDT, PH.D.
BALTIMORE

Among the numerous constituents of the blood stream few are more closely related to many of the fundamental processes of life than the amino-acids. Yet it was only within comparatively recent times (1913) that crystalline amino-acids [1] were actually isolated from the blood stream, and considerable confusion still seems to exist in regard to the amount of amino-acid nitrogen in normal and pathologic blood. Thus in a recent text on biochemistry [2] the statement is found that "in diabetes mellitus there is an accumulation of amino-acids in the blood and a corresponding increased excretion into the urine. Again in nephritis there is an accumulation of amino-acids in the blood." On another page of the same book one finds the statement that "amino-nitrogen rarely rises in the blood. Even during severe nephritis there is no characteristic increase in amino-nitrogen." In a recent book on blood chemistry,[3] the author said that "a definite rise in the amino-acid content of the blood appears only to have been recognized in acute yellow atrophy," whereas another author on the same subject [4] stated that "they have been found to be increased in nephritis but the clinical value of the determination is uncertain." Other writers of textbooks also indicate that the amino-acid nitrogen is increased in severe nephritis.[5] However, in their early work on the metabolism of the amino-acids, Folin and Berglund [6] pointed

* Submitted for publication, Jan. 23, 1929.

* From the Biochemical Laboratory of Mercy Hospital and the Department of Biological Chemistry of the University of Maryland School of Medicine.

1. Abel, J. J.; Rowntree, L. G., and Turner, B. B.: Tr. Am. A. Phys., May 6, 1913, p. 4.

2. Morse, W.: Applied Biochemistry, ed. 2, Philadelphia, 1927, pp. 542 and 837.

3. De Wesselow, O. L. V.: The Chemistry of the Blood in Clinical Medicine, New York, 1924, p. 24.

4. Kilduffe, R. A.: The Clinical Interpretation of Blood Chemistry, Philadelphia, Lea & Febiger, 1927, p. 96.

5. Hawk, P. B., and Bergeim, O: Practical Physiological Chemistry, ed. 9, Philadelphia, 1927, p. 357. Rehfuss, M. E.: Diagnosis and Treatment of Diseases of the Stomach, Philadelphia, W. B. Saunders Company, 1927, p. 1086. Myers, V. C.: Practical Chemical Analysis of the Blood, ed. 2, St. Louis, C. V. Mosby Company, 1924, p. 32.

6. Folin, O.: Laboratory Manual of Biological Chemistry, ed. 4, New York, D. Appleton & Company, 1925, p. 291. Berglund, H.: Nitrogen Retention in Chronic Intestinal Nephritis, J. A. M. A. **79**:1375 (Oct. 21) 1922.

out that the deaminization process is so fundamental that few conditions will be found in which the amino-nitrogen varies much from the normal. Papers in the current literature are equally as confusing as the statements in many of the textbooks and will be discussed in connection with the data from the laboratory.

This situation is due, probably, to the variety of methods which have been utilized for the determination of the amino-acids of the blood, viz., the "ninhydrin" reaction of Abderhalden, the Sörenson titration method, the gasometric method of van Slyke, the colorimetric reaction of Folin, etc., and the various methods which have been used for the preparation of the protein-free filtrates. Hence the exact amount of amino-acid nitrogen in an individual specimen will depend on the nature of the method that was used for the analysis. While this fact, however, may not vitiate completely the conclusions drawn from an individual paper, the data would hardly be comparable with those of another work in which a different analytic procedure was utilized.

The colorimetric method of Folin [7] in which sodium beta-naphthoquinone 4-sulphonate is used as the color reagent avoids many of the errors and difficulties inherent in the other methods for the determination of the amino-acid nitrogen of the blood, and as the method is adaptable to hospital routine it was used exclusively in this work. During the last two years, about 500 determinations have been made of the amino-acid nitrogen of the blood taken during fasting from patients with a considerable diversity of disease. The diagnoses taken from the charts of the patients were primarily clinical, although a few were confirmed by postmortem observations, and especial attention was given to those conditions in which uncertainty seems to exist as to the actual amino-acid content of the blood.

The amino-acid nitrogen of the blood specimens representing a considerable variety of diseases was found to be remarkably constant and showed but little variation from the normal range as found in healthy adults. In many diseases, such as uremia, diabetes, pneumonia, pernicious anemia, hepatic insufficiency, etc., in which the amino-acid nitrogen is reported to be appreciably elevated, normal results were obtained in all cases. Pathologic variations in the content of amino-acid nitrogen, among the cases examined in the laboratory, were found only in leukemia and acute yellow atrophy of the liver. In addition, it can be stated definitely from a survey of the literature that the amino-acids are also increased in polycythemia vera, and as a result of such hepatic poisons as hydrazine, synthalin, chloroform, etc., while large doses of insulin produce a decrease in the amino-acid nitrogen of the blood.

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7. Folin, O.: J. Biol. Chem. **51**:377, 1922.

EXPERIMENTAL METHODS

Folin's colorimetric method was used for the determination of the amino-acid nitrogen of the blood, and all precautionary measures were taken to insure accuracy of results. In order to avoid any postalimentary hyperamino-acidemia, the blood specimens were collected in the morning before breakfast and after a twelve hour fast in tubes containing about 10 mg. of lithium oxalate. The protein-free filtrates were immediately prepared according to Haden's[8] modification of the original Folin-Wu technic, in which twelve hundredth-normal sulphuric acid is used instead of the two-third normal acid. During the last few years, several thousand filtrates have been prepared in the laboratory by this method with excellent results; the filtrates always come through rapidly and are invariably clear and colorless. The filtrates, of course, were used for the other chemical analyses also. Ten cubic centimeters of the filtrate was used for each determination, and two amino-acid standards were prepared and matched with each other in the colorimeter in each run. If the standards checked with each other they were read against the unknown preparations.

REAGENTS

The stock amino-acid solution containing 0.1 mg. of amino-acid nitrogen per cubic centimeter was prepared by dissolving 0.1339 Gm. of glycine (Pfanstiehl) in tenth-normal hydrochloric acid containing 0.5 Gm. of sodium benzoate, and the solution was then diluted to 250 cc. with tenth-normal hydrochloric acid. The standard amino-acid solution was prepared by diluting 175 cc. of the stock solution to 250 cc. with the tenth-normal hydrochloric acid. This standard has been compared colorimetrically and found to check closely with the standard glycine solutions in use in two other laboratories. The special sodium carbonate solution was prepared by diluting 50 cc. of a saturated solution with distilled water until 8.5 cc. were exactly equivalent to 20 cc. of tenth-normal hydrochloric acid, with methyl red as the indicator. The acetic acid-acetate and sodium thiosulphate solutions were also prepared according to the directions of Folin.[7] The sodium naphthoquinone 4-sulphonate of various manufacturers was found not to be of uniform quality, and the specified amount of one particular brand would hardly take care of the amino-acid nitrogen found in 10 cc. of a protein-free filtrate. However, a satisfactory product was secured from the Eastman Kodak Company and was tested out in the following manner: A series of amino-acid standards were prepared by diluting aliquot quantities of the stock solution to various volumes with tenth-normal hydrochloric acid in such a manner that 1 cc. of each of the diluted glycine solutions contained the amount of amino-acid nitrogen as given in the first column of table 1. The figures, however, have been multiplied by 100 in order to make them comparable with the figures obtained from blood filtrates where the calculations are based on milligrams of amino-acid nitrogen per hundred cubic centimeters of blood. The amino-acid nitrogen in each glycine solution was determined in the usual manner and compared with the regular standard. Then a series of determinations were made in which various amounts of the freshly prepared beta-naphthoquinone solution was added to the different glycine solutions and then matched in the colorimeter against the usual amino-acid standard. The data are given in table 1 and show that each cubic centimeter of the 0.5 per cent beta-naphthoquinone solution takes care of from about 0.08 to 0.1 mg of amino-acid nitrogen. Thus, if the blood is suspected to be high in amino-acids the filtrate should

8. Haden, R. L.: J. Biol. Chem. **56**:469, 1923.

be diluted, or more of the quinone reagent should be used in the determination. By carefully following the directions of Folin in every detail, I have never encountered any difficulties with the method, and uniformly satisfactory results were always obtained.

RESULTS

In regard to the average amount of amino-acid nitrogen in the blood of healthy adults, various figures have been reported; the inconsistencies

TABLE 1.—*The Effect of Varying the Amounts of Amino-Acid Nitrogen and the Naphthoquinone Reagent*

Amino-Acid Nitrogen Added, Mg.*	1 Cc. Naphthoquinone			2 Cc. Naphthoquinone			3 Cc. Naphthoquinone		
	Colorimeter Reading, Mm.	Amino-Acid Nitrogen Found, Mg.*	Difference, Mg.*	Colorimeter Reading, Mm.	Amino-Acid Nitrogen Found, Mg.*	Difference, Mg.*	Colorimeter Reading, Mm.	Amino-Acid Nitrogen Found, Mg.*	Difference, Mg.*
42.0	13.0	10.8	—31.2	6.5	21.5	—20.5	4.7	29.8	—12.2
31.5	13.0	10.8	—20.7	6.5	21.5	—10.0	5.3	26.4	— 5.1
21.0	13.5	10.4	—10.6	6.6	21.2	+ 0.2	6.8	20.6	— 0.5
14.0	13.5	10.4	— 3.6	10.2	13.7	— 0.3	10.0	14.0	0.0
10.7	16.0	8.8	— 1.9	13.0	10.8	— 0.1	13.0	10.8	+ 0.1
8.4	16.1	8.7	+ 0.3	15.5	9.0	+ 0.6	16.0	8.8	+ 0.4
7.0	22.0	6.4	— 0.6	20.0	7.0	0.0	20.2	6.9	— 0.1
6.0	24.0	5.8	— 0.2	22.5	6.2	+ 0.2	24.0	5.8	— 0.2
5.0	29.0	4.8	— 0.2	28.0	5.0	0.0	27.0	5.2	+ 0.2
4.0	33.0	4.2	+ 0.2	32.5	4.3	+ 0.3	33.0	4.2	+ 0.2

* Each figure has been multipled by 100.

TABLE 2.—*Amino-Acid Nitrogen Content of Normal Blood*

Author of Report	Mg. per 100 Cc. Blood		
	Minimum	Maximum	Average
Folin, O., and Berglund, H., 12 young men [6]	5.7	7.8	6.4
Greene, C. H.; Sandiford, K., and Ross, H. (J. Biol. Chem. **53**: 845, 1924) 20 normal persons	5.2	7.2	6.37
Fownweather, F. S., and Gordon, J. (Brit. J. Exper. Path. **8**: 93, 1927) 15 normal cases	4.9	8.1	6.46
McClure, C. W., and Huntsinger, M. E. (J. Biol. Chem. **74**: 1, 1928) 15 normal persons	4.8	7.5	6.6
Hoeffel, G. N., and Moriarty, M. E. (Am. J. Dis. Child. **27**: 64 [Jan.] 1924) 14 normal adults	6.4	8.1	7.04
Wowsi, M., and Gelbird, J. (Ztschr. f. d. ges. exper. Med. **51**: 518, 1926) 30 normal persons	5.3	8.0	....
Schmidt, E. G. (this paper) 25 adults	4.8	7.8	6.3

are probably due to the different procedures which were used for the analyses. The more reliable reports of the various investigators who have utilized the Folin colorimetric method for the determination of the amino-acid nitrogen of the blood have been collected in table 2. The general average is thus seen to be from 6.3 to 6.5 mg. of amino-acid nitrogen per hundred cubic centimeters of blood. The results of the analysis of the blood of twenty-five normal adults and adults with minor surgical conditions were found to average 6.3 mg. and to range from 4.8

to 7.8 mg. of amino-acid nitrogen per hundred cubic centimeters of blood, and are thus in good agreement with most of the figures in table 2.

The results of the analysis of the pathologic specimens of blood are given in table 3 and include the number of cases of each disease and

TABLE 3.—*The Amino-Acid Nitrogen Content of the Blood in Various Diseases*

Diagnoses	Number of Cases	Mg. per 100 Cc. Minimum	Mg. per 100 Cc. Maximum	Mg. per 100 Cc. Average
Appendicitis (chronic and acute)	7	5.8	7.0	6.3
Alcoholism (chronic and acute)	9	5.6	6.7	6.2
Gastric ulcer	3	5.0	6.7	6.4
Intestinal obstruction	7	6.4	6.7	6.6
Gastritis	2	6.5	6.5	6.5
Achlorhydria	2	5.5	5.7	5.6
Gastroptosis	1	...	...	6.1
Chemical poisoning (lead, arsenic, carbon monoxide, etc.)	5	5.5	6.7	6.0
Colitis	2	6.0	6.4	6.2
Malnutrition	3	6.4	6.5	6.4
Adhesions	4	5.8	7.2	6.6
Pneumonia (lobar and bronchopneumonia)	17	4.7	8.0	6.1
Grip, laryngitis, bronchitis, etc.	7	6.0	6.6	6.3
Rheumatic cardiovascular disease	2	5.7	5.9	5.8
Syphilitic cardiovascular disease	2	6.1	6.8	6.5
Arteriosclerotic cardiovascular disease	20	5.0	8.3	6.5
Hypertensive cardiovascular disease	10	5.6	7.4	6.6
Hypertension (essential and paroxysmal)	14	5.6	7.4	6.4
Hypotension	2	6.1	6.1	6.1
Neurocirculatory asthenia	2	5.8	6.1	6.0
Aneurysm of aorta	2	6.4	6.6	6.5
Cerebral accidents (hemorrhages, thrombosis, etc.)	11	5.6	7.6	6.7
Angina pectoris	2	6.9	8.0	7.5
Myocardial degeneration with cardiac decompensation	8	4.1	6.9	5.8
Gynecologic and obstetric conditions as pregnancy, toxemia, cysts, fibroids, pyelitis salpingitis, etc.	40	4.0	7.2	6.0
Neurologic conditions	18	5.0	6.7	6.2
Benign hypertrophy of prostate	9	5.6	7.0	6.5
Peritonitis	4	5.2	7.0	6.3
Hernia (various types)	9	5.8	7.0	6.4
Syphilis (various types)	8	5.8	6.8	6.2
Neoplasms (benign and malignant)	10	4.1	6.4	6.0
Gallbladder diseases	8	5.5	7.0	6.0
Arthritis (various types)	4	5.8	6.3	6.1
Serum reaction	1	...	...	7.0
Neuritis	1	...	...	4.9
Gout	4	5.0	7.0	6.0
Retinitis pigmentosa	1	...	...	8.2
Hemolytic jaundice	1	...	...	8.2
Nephrosis	3	5.5	5.7	5.6
Hemiplegia	1	...	...	6.8
Thyroid dysfunction	6	5.7	6.7	6.0
Anemia (secondary and pernicious)	10	5.0	8.0	6.4
Cirrhosis of the liver	5	6.0	7.8	7.2
Diabetes mellitus—blood sugar 44 (insulin shock)	1	...	...	4.5
Diabetes mellitus—blood sugar 100 to 150	22	5.2	7.0	6.3
Diabetes mellitus—blood sugar 150 to 200	25	4.5	6.9	5.0
Diabetes mellitus—blood sugar 200 to 250	15	4.7	6.9	6.2
Diabetes mellitus—blood sugar 250 to 300	15	5.8	6.8	6.3
Diabetes mellitus—blood sugar 300 to 400	6	6.1	7.6	6.6
Diabetes mellitus—blood sugar 400 to 600	2	6.4	6.6	6.5
Tuberculous meningitis	1	...	...	6.9
Renal diseases (from table 5)	35	4.5	8.8	6.3
Miscellaneous and outpatients	40	5.8	7.2	6.3
Average of 449 determinations	..	...	...	6.3
Normal persons and those undergoing minor operations	25	4.8	7.8	6.3

the minimal, maximal and average content of amino-acid nitrogen. In spite of the wide variety of diseases represented in the specimens subjected to examination, the blood was found to be remarkably constant in amino-acids and did not deviate appreciably from the normal range found in healthy adults. The figures were found to range from 4 to 8.3 mg.,

with an average amino-acid nitrogen of 6.3 mg., the same average as was established for normal blood. The only case in which the amino-acid appreciably exceeded 8 mg. was one of arteriolar nephritis (table 5, no. 14) which showed 8.8 mg. of amino-acid per hundred cubic centimeters of blood, the blood having been taken just prior to death. This value may be explained in the light of the recent work of Becker,[9] who pointed out that the amino-acids of the blood begin to increase just prior to death, and that the rise is rapid soon after life ceases. However, most of the cases in which the amino-acid was slightly in excess of 8 mg. (from 8 to 8.3 mg.) were found to yield normal values on reexamination within a few days. The distribution of amino-acid nitrogen and frequency of occurrence of the various values are given in table 4 and indicate that 180 determinations, or 40.09 per cent, occurred between 6 and 6.4 mg., and therefore 6.3 mg. is close to the probable average amino-acid nitrogen content of the blood. The results in regard

TABLE 4.—*The Distribution of Amino-Acid Nitrogen and Frequency of Occurrence*

Amino-Acid Nitrogen, Mg. per 100 Cc.	Number of Occurrences	Per Cent
4.0 to 4.4	2	0.44
4.5 to 4.9	13	2.89
5.0 to 5.4	40	8.89
5.5 to 5.9	70	15.59
6.0 to 6.4	180	40.09
6.5 to 6.9	84	18.71
7.0 to 7.4	39	8.68
7.5 to 7.9	11	2.45
8.0 to 8.4	8	1.78
8.5 to 8.8	1	0.22

to certain diseases merit further discussion and will be taken up in connection with the reports of other workers.

Results in Certain Diseases.—Nephritis: As previously pointed out, the rather scanty literature on the subject of the possible retention of amino-acids in renal disease is full of conflicting statements. The earlier work was carried out with the gasometric method of van Slyke on filtrates which had been deproteinized in a variety of ways. Thus Bock [10] found that among the numerous diseases in which the amino-acids were increased the most pronounced variations from the normal occurred in nephritis, and his results are quoted in most texts on biochemistry and chemical pathology. Okada and Hayashi [11] confirmed the results of Bock on patients with severe uremia, and they also found increased amino-acids in the blood of dogs after ligating the ureters or

9. Becker, E., and Herrman, E.: München. med. Wchnschr. **72**:1069 and 2178, 1925.

10. Bock, J. C.: J. Biol. Chem. **28**:357, 1916; ibid. **29**:191, 1916.

11. Okada, S., and Hayashi, T.: J. Biol. Chem. **51**:121, 1922.

extirpating the kidneys. Blau,[12] Desqueyroux,[13] Hulse and Strauss [14] and others, also found increased amino-acids in advanced renal disease, whereas Losee and van Slyke [15] and Morse [16] found no marked deviations from the normal in pre-eclamptic toxemia, eclampsia, nephritic toxemia and similar conditions. In general, the results secured with the colorimetric method of Folin yielded normal results in most diseases. Thus Folin and Berglund,[6] in a small series of cases, found that the amino-acids did not parallel the retention of urea, while Greene, Sandiford and Ross [17] found that "there is no significant departure from the normal and no apparent correlation between the amino-acids and degree of renal insufficiency." Feinblatt and Shapiro [18] reported that "while in an individual instance urea retention is apt to be accompanied by hyperamino-acidemia, this association is just as often completely lacking" and that, as a rule, normal values are usually obtained. Bandler and Killian [19] reported a case of cancer of the bladder in which the amino-acid nitrogen showed a terminal rise to 12 mg. Looney [20] found, in an individual case of mercuric chloride poisoning with retention and anuria, that the amino-acids did not increase until shortly before death. However, in a recent investigation of the rôle of the liver in amino-acid metabolism, Wowsi and Gelbird [21] noted an increase of amino-acids in the blood in cases of cancer (especially of the stomach and liver), syphilis, acute yellow atrophy of the liver and severe hepatitis as well as in leukemia, uremia, pneumonia, and other diseases.

In table 5 is listed a series of blood chemistry studies of thirty-five patients with various types and in diverse stages of renal disease. The blood urea values ranged from 19 to 610 mg., and the creatinine from 1.5 to 15 mg. per hundred cubic centimeters of blood. The average amino-acid nitrogen of the thirty-five patients was found to be 6.3 mg., exactly normal, with a minimum of 4.5 and a maximum of 8.8 mg.; therefore, regardless of the degree of renal damage, the amino-acid nitrogen content of the blood showed no appreciable departure from the normal values. In only one case did the amino-acid nitrogen exceed 8 mg. (no. 14); the blood for that determination, however, was taken just before death. In connection with such conditions as intestinal

12. Blau, N. F.: J. Biol. Chem. **56**:861 and 867, 1923.
13. Desqueyroux, J.: Ann. de méd. **13**:20 (Jan.) 1923.
14. Hulse, W., and Strauss, H.: Ztschr. f. d. ges. exper. Med. **39**:442, 1924.
15. Losee, J. R., and van Slyke, D. D.: Am. J. M. Sc. **158**:94, 1917.
16. Morse, A.: Bull. Johns Hopkins Hosp. **28**:199, 1917.
17. Greene, C. H.; Sandiford, K., and Ross, H.: J. Biol. Chem. **53**:845, 1924.
18. Feinblatt, H. M., and Shapiro, L.: Amino-Acid Content of Blood in Various Pathologic Conditions, Arch. Int. Med. **34**:690 (Nov.) 1924.
19. Bandler, C. G., and Killian, J. A.: J. Urol. **19**:1, 1928.
20. Looney, J. M.: J. Biol. Chem. **70**:513, 1926.
21. Wowsi, M., and Gelbird, J.: Ztschr. f. d. ges. exper. Med. **51**:518, 1926.

obstruction, pneumonia, etc., in which the urea content is considerably elevated, no increase in amino-acids was noted.

Pernicious Anemia: Several investigators, especially Gettler and Lindeman [22] and Gorchkoff, Grigorieff and Koutoursky [23] have reported increases in the amino-acid content of the blood in pernicious anemia, whereas others [24] found normal values. Table 3 includes ten cases of anemia of various types, and the amino-acid nitrogen was found to average 6.4 mg. with no deviations from the normal range.

TABLE 5.—*The Amino-Acid Nitrogen Content of Blood in Renal Disease*

		Blood Chemistry		
	Diagnosis	Urea Mg.	Creatinine Mg.	Amino-Acid Nitrogen Mg.
1	Acute nephrosis; mercuric chloride poisoning	610	8.4	6.1
2	Chronic diffuse glomerular nephritis	585	6.4	7.4
3	Chronic interstitial nephritis	575	8.4	6.1
4	Pyonephrosis	565	8.0	7.8
5	Pyonephrosis	555	12.0	6.7
6	Pyonephrosis	485	9.0	4.7
7	Acute nephrosis; mercuric chloride poisoning	480	9.8	5.6
8	Acute nephrosis; mercuric chloride poisoning	425	6.0	6.7
9	Chronic interstitial nephritis	415	10.0	5.2
10	Pyonephrosis	405	5.6	5.0
11	Chronic diffuse glomerular nephritis	405	6.4	6.4
12	Acute nephrosis; mercuric chloride poisoning	395	9.4	7.4
13	Acute nephritis	385	9.2	5.8
14	Anteriolar nephritis	340	8.0	8.8
15	Pyonephrosis	333	12.0	5.4
16	Acute nephrosis; mercuric chloride poisoning	320	7.0	7.0
17	Chronic nephritis	277	15.0	5.1
18	Chronic diffuse glomerular nephritis	247	6.4	6.4
19	Chronic diffuse glomerular nephritis	215	7.0	6.3
20	Chronic diffuse glomerular nephritis	215	6.4	6.1
21	Bilateral pyelonephritis (advanced)	200	3.4	6.3
22	Chronic diffuse glomerular nephritis	200	10.0	7.0
23	Acute nephrosis; mercuric chloride poisoning	180	5.0	6.1
24	Chronic interstitial nephritis	166	2.2	6.2
25	Chronic diffuse glomerular nephritis	166	4.8	5.4
26	Chronic diffuse glomerular nephritis	150	3.8	4.5
27	Bilateral pyonephrosis	150	2.6	6.4
28	Acute nephritis	149	1.6	7.7
29	Chronic arteriolar nephritis	104	1.9	7.4
30	Acute focal glomerular nephritis	98	2.4	6.4
31	Acute focal glomerular nephritis	94	2.8	7.2
32	Chronic arteriolar nephritis	73	1.9	6.4
33	Chronic arteriolar nephritis	61	1.5	6.0
34	Chronic interstitial nephritis	40	1.4	6.3
35	Chronic interstitial nephritis	19	1.5	5.8
	Average	...	....	6.3

Diabetes Mellitus: In diabetes mellitus a number of investigators, including Labbé and Violle,[25] Galambos and Tausz,[26] Wolpe,[27]

22. Gettler, A. O., and Lindeman, E.: Blood Chemistry of Pernicious Anemia, Arch. Int. Med. **26**:453 (Oct.) 1920.

23. Gorchkoff, M.; Grigorieff, W., and Koutoursky, A.: Compt. rend. Soc. de biol. **76**:454, 1914.

24. Greene, Sandiford and Ross (footnote 17). Feinblatt and Shapiro (footnote 18).

25. Labbé, H., and Violle, K.: Compt. rend. Acad. d. sc. **154**:73, 1912.

26. Galambos, A., and Tausz, B.: Ztschr. f. klin. Med. **77**:14, 1913; ibid. **80**: 381, 1914.

27. Wolpe, G.: München. med. Wchnschr. **71**:363, 1924.

Desqueyroux [13] and others, found increased amino-acids with the van Slyke method, whereas Greene, Sandiford and Ross,[17] Feinblatt and Shapiro,[18] von Falkenhausen [28] and others found no increase in the amino-acids with the Folin method. Table 3 includes the amino-acid nitrogen content of eighty-five diabetic patients in various stages of insulin therapy with blood sugar values ranging from 100 to 600 mg. per hundred cubic centimeters of blood. The amino-acid nitrogen of these specimens of blood from diabetic patients was found to range from 4.5 to 7.6 mg. with an average of 6.3 mg. for the eighty-five determinations, and all were well within the normal range. This series also includes a young diabetic child in coma from insulin shock whose blood sugar was 44 mg. and the corresponding amino-acid nitrogen 4.5 mg., which might indicate that an overdose of insulin produces a decrease in the amino-acids of the blood. This observation would be in keeping with the experiments of Luck, Morrison and Wilbur [29] who demonstrated that subconvulsive doses of insulin lowered the amino-acid content of the blood of rabbits, rats and human beings; the maximum decrease was from 2.5 to 3 mg. Greene, Sandiford and Ross [17] stated that insulin has no effect on the amino-acids; however, Tashiro,[30] Wiechmann,[31] Wolpe [27] and others agreed that insulin produces a reduction in the amino-acids of the blood. On the other hand, parenteral administrations of such antidiabetic substances as synthalin [32] and other insulin substitutes [33] have been found to produce an increase in the amino-acids of the blood, which was attributed to injury to the liver as exhibited by a decreased ability to deaminize injected glycine. In this connection Lewis and Izume [34] found that the subcutaneous administration of hydrazine sulphate to fasting rabbits often produced fatty degeneration of the liver as shown by a marked rise in the amino-acids of the blood, while Marshall and Rowntree [35] found that phosphorus and especially chloroform also produced an amino-acidemia and a decrease in blood urea.

Hepatic Insufficiency: My views of the metabolism of the amino-acids primarily center around the functions of the liver and rest largely

28. Von Falkenhausen, M. F.: Arch. f. exper. Path. u. Pharmakol. **103**:322, 1924.

29. Luck, J. M.; Morrison, G., and Wilbur, L.: J. Biol. Chem. **77**:151, 1928.

30. Tashiro, K.: Tohoku, J. Exper. Med. **7**:221, 1926.

31. Wiechmann, E., and Dominick, M.: Arch. f. klin. Med. **153**:1, 1926.

32. Blatherwick, N. R.; Sahyun, M., and Hill, E.: J. Biol. Chem. **75**:671, 1927.

33. Bischoff, F.; Blatherwick, N. R., and Sahyun, M.: J. Biol. Chem. **77**:467, 1928.

34. Lewis, H. B., and Izume, S.: J. Biol. Chem. **71**:33, 1926.

35. Marshall, E. K., Jr., and Rowntree, L. G.: J. Exper. Med. **22**:333, 1915.

on the evidence presented by the work of van Slyke,[36] Folin [37] and Mann [38] and others. On complete removal of the liver of dogs, Mann and his collaborators demonstrated that there resulted a complete cessation of deaminization and a resultant increase in the amino-acid content of the blood. Evidence has been presented to show that in diseases of hepatic origin there is an increased content of amino-acids,[39] but Greene, Sandiford and Ross [17] found no increase in a number of cases of cirrhosis or chronic hepatitis, and the limited data in table 3 are in conformity with the latter statement. However, Wowsi and Gelbird,[21] who also used the method of Folin, found that the amino-acids were increased in syphilitic and arsenical hepatitis and especially in primary cancer of the liver and in acute yellow atrophy, whereas normal values were secured in infectious and toxic jaundice. The fact is well known that in acute yellow atrophy there is found a marked increase in the amino-acids of the blood and urine.[40] In the single case of acute yellow atrophy of the liver

TABLE 6.—*Amino-Acid Nitrogen Content in Leukemia*

Number	Date	Amino-Acid Nitrogen, Mg.	Leukocyte Count
1.	3/ 1/28	10.3	540,000
2.	3/ 8/28	9.2	76,800
3.	6/20/28	8.0	230,000
4.	11/21/28	4.9	7,900
4.	11/22/28	5.4	5,900
4.	11/28/28	7.8	59,000
5.	12/27/28	7.2	80,000

reported in this paper the following laboratory observations per hundred cubic centimeters of blood were secured: amino-acid nitrogen, 16.5 mg.; urea, 29 mg.; nonprotein nitrogen, 57 mg.; sugar, 50 mg., and sodium chloride, 380 mg. The van den Bergh reaction was prompt direct positive with 22 mg. of bilirubin per hundred cubic centimeters of serum, and the icterus index was 200. These figures are typical of acute yellow atrophy.

36. Van Slyke, D. D.: The Harvey Lectures, 1915-1916, vol. 11, p. 146.

37. Folin, O.: Physiol. Rev. **2**:460, 1922.

38. Mann, F. C.: Medicine **6**:419, 1927.

39. Rowntree, L. G.; Marshall, E. K., and Chesney, A. M.: Tr. Am. A. Phys. **29**:586, 1914.

40. Wolpe (footnote 27). Feigle, J., and Luce, H.: Biochem. Ztschr. **79**:162, 1917. Roman, B.: Acute Yellow Atrophy of Liver, Arch. Path. **4**:399 (Sept.) 1927. Stadie, W. C., and van Slyke, D. D.: Effect of Acute Yellow Atrophy on Metabolism and on Composition of the Liver, Arch. Int. Med. **25**:693 (June) 1920. Tileston, W., and Comfort, C. W.: The Total Nonprotein Nitrogen and the Urea of the Blood in Health and in Disease, as Estimated by Folin's Methods, ibid. **14**:620 (Nov.) 1914.

Polycythemia Vera (Erythremia): Greene and Conner [41] stated that true polycythemia is the converse of anemia in that it is characterized by a persistent increase in the red blood corpuscles with resultant plethora, and they found that the animo-acids are moderately (from 8 to 14.3 mg.) increased in the blood. Luck [42] also reported that the amino-acids are increased in polycythemia. No cases of polycythemia were encountered while this work was in progress.

Leukemia: In leukemia, particularly of the myelogenous type, the blood has been found to contain a moderate increase of amino-acid nitrogen.[43] It is said that in general the concentration of amino-acids parallels approximately the leukocyte count, and that there is some, but not necessarily a proportionate, increase in the basal metabolism.[44] While this work was in progress, five cases of lymphatic leukemia of various types were encountered, and the following data indicate that a small increase in amino-acid nitrogen is frequently found if associated with a high leukocyte count.

Certain phases of this work are still being continued.

SUMMARY

1. The amino-acid nitrogen content of normal adult blood, as determined by the Folin colorimetric method with sodium beta-naphthoquinone 4-sulphonate, was found to average 6.3 mg. and to range from 4.8 to 7.8 mg. per hundred cubic centimeters of blood.

2. The analysis of almost 500 specimens of blood representing a considerable diversity of disease proved that the concentration of amino-acids remains remarkably constant. The values range from 4 to 8.3 mg. with an average of 6.3 mg. per hundred cubic centimeters of blood.

3. The amino-acid nitrogen content of the blood was found to be frequently moderately increased in leukemia and greatly elevated in acute yellow atrophy of the liver. The amino-acids are also increased (no data in this paper) in polycythemia vera, and as a result of the administration of such hepatic poisons as hydrazine sulphate, synthalin, chloroform and phosphorus.

41. Greene, C. H., and Conner, H. M.: Diseases of the Liver: Comparative Study of Tests for Hepatic Function in Certain Diseases of the Hematopoietic System, Arch. Int. Med. **38**:167 (Aug.) 1920.

42. Luck, J. M.: J. Biol. Chem. **77**:13, 1928.

43. Okada and Hayashi (footnote 11). Martin, C. L.; Denis, W., and Aldrich, M.: Am. J. M. Sc. **160**:223, 1920.

44. Sandiford, K.; Boothby, M., and Giffen, H.: J. Biol. Chem. **55**:23, 1923.

FAILURE OF A DIABETIC PATIENT TO UTILIZE DRIED ARTICHOKE POWDER *

L. E. WESTCOTT, M.D.
AND
E. C. WISE, M.S.
KALAMAZOO, MICH.

For a number of years the use of artichokes has been of interest in the treatment of diabetic patients and has been discussed frequently in numerous papers. Root and Baker [1] fed twenty-five diabetic patients Jerusalem artichokes in addition to their regular diet. Occasionally, artichokes, a 15 per cent vegetable, were substituted for a 5 per cent vegetable. In some cases the artichokes were taken daily, in others on alternate days, and in one instance, only once a week. The average amount of uncooked artichokes taken per day amounted to 130 Gm. If we interpret their table correctly, seventeen patients increased their carbohydrate tolerance from 51 to 59 Gm. exclusive of approximately from 19 to 20 Gm. of carbohydrate, which was added as artichoke. The intake level for fat was slightly improved. In short, the calory intake was successfully increased from 1,353 to 1,501, or 148 calories, of which about 112 calories came from the artichokes. We might conclude that an additional tolerance of the levulose sugars over the dextrose sugars, amounting to approximately 30 Gm., is established. It must be mentioned, however, that the dosage of insulin was increased by 3 units per day. Additional evidence along this line was obtained when 100 Gm. of artichokes, replacing 15 Gm. of dextrose sugars, rendered the urine sugar-free. Another patient replaced the 5 per cent vegetable with artichokes in equivalent amount. This increased her carbohydrate intake by 10 Gm., and she became sugar-free.

Carpenter and Root [2] reported that when carbohydrate was fed in a comparative way, with the use of artichokes and potatoes, at a level of 205 Gm. of carbohydrate (of which 110 Gm. came from the two sources mentioned), about 10.5 Gm. of sugar was found in the urine of patients on the potato diet but none in that of those on the artichoke diet.

A reasonable interpretation of these experiments would lead us to conclude that there is a slightly greater tolerance for the levulose deriva-

* Submitted for publication, March 20, 1929.

1. Root, H. F., and Baker, M. L.: Inulin and Artichokes in the Treatment of Diabetes, Arch. Int. Med. **36**:125 (July) 1925.

2. Carpenter, T. M., and Root, H. F.: Utilization of Jerusalem Artichokes by Patient with Diabetes, Arch. Int. Med. **42**:64 (July) 1928.

tives in this form than for the usual dextrose carbohydrates, and that it might amount to as much as 30 Gm. per day.

Joslin[3] summarized as follows: "Twelve patients took an average of 92 grams of artichokes in addition to their regular diets . . . . without increasing glycosuria already present or producing glycosuria in patients previously sugar free. The average increase in carbohydrate was thus about 13 grams."

Our object in the work recorded in this paper was to study the qualitative aspect of this question with a diabetic patient who was not receiving insulin. In brief, we carefully determined the carbohydrate tolerance in the usual manner. We then dropped the carbohydrate intake just below the known tolerance and superimposed dried artichoke powder in weighed amounts and again determined the tolerance. We conclude that the tolerance is not appreciably increased by the artichokes.

REPORT OF CASE

J. C. P., a man, aged 22, unmarried, employed as a bank clerk, presented an unimportant past and family history. In August, 1927, he felt "run down" and received a tonic from his family physician. No urinary symptoms were noted at this time, and within a month he felt entirely well. In March, 1928, he began to feel exhausted during the morning and had not felt well since that time. In October, 1928, the urinary symptoms, pollakiuria, polyuria and polydipsia were first noted. Polyphagia accompanied these symptoms, and about the first of November the patient noticed a dry skin and dry mouth.

Examination.—Examination on Nov. 12, 1928, showed a blood sugar content of 254 mg. per hundred cubic centimeters and a urine sugar content of 6 per cent. The urine was negative for diacetic acid. The patient was advised to rest and was placed on a restricted diet. He was rendered sugar-free on a diet containing about 140 Gm. of available dextrose daily (without the use of insulin). At this time, Dec. 6, 1928, the patient consented to take part in the following experiment.

Experimental Conditions.—The basal diet of the subject was planned to be similar to the diet given in "Diets of University of Michigan Hospital."[4] The diet was made up of beef, pork, cream, butter, mayonnaise (diabetic), bacon, eggs, lettuce, celery, squash, peas, corn flakes and Uneeda biscuits. The diet was so arranged as to give approximately equal amounts of dextrose at each of the three meals and yielded daily about 200 Gm. of fat, 100 of carbohydrate and 70 of protein (table 1). When it was desired to alter the carbohydrate content this was usually done by varying the number of Uneeda biscuits. The food values of the materials mentioned were determined by analysis by the official methods of the Association of Official Agricultural Chemists.[5] Water, coffee and saccharin were allowed in addition to the foods mentioned. The materials for each meal were weighed with an accuracy of ± 1 Gm.

Once the diet was adjusted to the proper level it was kept constant within narrow limits. Meals were served at the same time each day.

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3. Joslin: Treatment of Diabetes Mellitus, ed. 3, Philadelphia, Lea & Febiger, p. 549.

4. Diets of University of Michigan Hospital, p. 66.

5. Official Methods of Analysis, A.O.A.C., ed. 2.

The artichoke powder was prepared by slicing washed artichokes and drying them in a vacuum drier. The analysis of this powder showed the following composition: moisture, 8.4; ash, 4.2; protein, 7.8; fiber, 3; fat, 1.2, and total carbohydrate by acid hydrolysis, 75.4 per cent. It should be pointed out that the product fed contained no inulin so that the carbohydrate consisted essentially of soluble sugars, levulose and inuloids.

The urine was collected under toluene. All analyses were made on twenty-four hour samples, the daily sample ending before breakfast at 8 a. m. Nitrogen was determined by the Kjeldahl method and dextrose by the method of Benedict.

Samples of feces were collected and analyzed at once for carbohydrate,[6] nitrogen and fat.[7]

TABLE 1.—*Basal Food Intake*

Day	Protein, Gm.	Fat, Gm.	Carbohydrate Gm.	Available Dextrose, Gm.	Water, Cc.	Weight, Pounds	Artichoke Increment Added to Basal Diet in Grams of Carbohydrate
1	62	218	52	110	1,510	118	..
2	62	218	52	110	1,330	119	..
3	65	218	52	112	1,750	119	..
4	65	218	66	126	1,150	121	..
5	65	218	96	155	1,700	121	..
6	65	218	125	180	1,550	119	..
7	59	222	155	213	1,350	121	..
8	63	236	174	240	1,450	121	..
9	74	237	137	201	1,600	118	..
10	70	236	105	169	1,250	116	..
11	69	236	105	169	1,500	115	..
12	69	236	105	169	1,400	116	..
13	69	236	105	169	1,200	115	30
14	69	236	105	169	1,500	116	19
15	69	236	105	169	1,150	118	19
16	69	236	105	169	1,000	118	..
17	69	236	105	169	1,000	116	..
18	69	236	105	169	1,110	117	..
19	69	236	105	169	1,700	119	..
20	69	236	105	169	1,750	120	..
21	64	236	96	156	1,350	119	19
22	69	236	101	165	1,200	118	19
23	69	236	105	169	1,950	117	22
24	69	236	105	169	1,750	119	22
25	69	236	105	169	1,700	118	22
26	69	236	105	169	1,150	117	..
27	69	236	105	169	1,350	118	..
28	69	236	105	169	1,150	117	..
29	69	236	105	169	1,800	118	..
30	69	236	105	169	1,200	118	..

The data collected on the urine and feces are shown in tables 2 and 3. In no case were appreciable quantities of reducing sugars or hydrolyzable sugars found in the feces. The water intake and daily weight of the subject are also recorded.

COMMENT

Starting with a basal diet consisting of 62 Gm. of protein, 218 of fat, and 52 of carbohydrate, we increased the intake of available dextrose by the addition of Uneeda biscuits until on the fifth day it was found necessary to revise the basal diet upward to avoid feeding a number of

6. Hawk and Bergeim: Physiological Chemistry, ed. 9, Philadelphia, P. Blakiston's Son & Company, p. 866.

7. Hawk and Bergeim (footnote 6, p. 329).

Uneeda biscuits. The revised diet, which was made up of the same materials used before but in increased amounts, contained: protein, 69 Gm.; fat, 236 Gm.; carbohydrate, 105 Gm., and total available dextrose,

TABLE 2.—*Urinalysis*

Day	Volume, Cc.	Specific Gravity	Acetone	Nitrogen Gm.	Sugar, Gm.
1	1,370	1.019	None	10.9	0
2	1,370	1.015	None	8.2	0
3	1,660	1.020	None	14.9	0
4	1,060	1.020	Trace	10.9	0
5	1,470	1.018	Trace	7.8	0
6	1,350	1.015	None	8.4	0.4
7	1,350	1.021	None	9.0	4.8
8	1,200	1.029	None	8.7	29.5
9	1,690	1.022	None	10.2	22.7
10	1,200	1.022	None	8.6	14.2
11	850	1.026	None	9.2	8.7
12	1,000	1.024	None	9.6	7.0
13	980	1.029	None	10.5	17.0
14	1,030	1.025	None	7.9	14.0
15	1,027	1.027	None	9.1	15.4
16	1,190	1.026	None	10.7	18.9
17	660	1.030	None	6.4	13.8
18	1,570	1.019	None	12.7	7.8
19	1,750	1.017	None	10.8	7.5
20	960	1.024	None	10.0	4.6
21	1,470	1.018	None	10.5	3.5
22	1,200	1.018	None	9.1	0
23	1,760	1.015	None	9.6	0
24	1,750	1.017	None	9.2	3.4
25	1,580	1.019	None	9.4	8.5
26	1,210	1.022	None	8.6	6.2
27	1,170	1.022	None	10.3	6.9
28	1,140	1.021	None	9.1	4.5
29	1,270	1.020	None	10.7	5.0
30	1,260	1.020	None	10.2	5.4

TABLE 3.—*Data Collected on Feces and Blood*

Day	p_H *	Weight. Gm.	Nitrogen, Gm.	Fat, Gm.	Blood	
					Sugar Mg. per Hundred Cubic Centimeters	Nonprotein Nitrogen, Mg. per Hundred Cubic Centimeters
1	.....	84	1.1	4.2	...	..
2	.....	84	1.1	4.2	...	..
3	.....	84	1.1	4.2	...	..
4	.....	84	1.1	4.2	97	50
5	.....	119	0.8	5.4	...	..
6	.....	119	0.8	5.4	...	..
7	.....	119	0.8	5.4	...	..
8	.....	119	0.8	5.4	...	..
9	6.88†	119	0.8	5.4	...	..
10	6.45†	119	0.8	5.4	...	..
11	6.00†	221	1.3	4.5	190	55
12	.....	221	1.3	4.5	...	..
13	.....	221	1.3	4.5	...	..
14	.....	56	1.3	3.9	...	..
15	.....	56	1.3	3.9	...	..

* The p_H of the feces was recorded as follows: Sixteenth day, 7.38; eighteenth, 7.4; nineteenth, 7.44; twenty-third, 7.28; twenty-seventh, 7.48; twenty-ninth, 7.4.

† Diarrhea.

169 Gm. On the sixth day, with the addition of 11 Gm. of carbohydrate and a total dextrose intake of 180 Gm., the first trace of glycosuria was observed, and was close to the tolerance of the patient. Had this

diet (180 Gm. of available dextrose) been continued, the subject would undoubtedly have excreted several grams of dextrose daily. On the seventh and eighth days, however, the carbohydrate increment was increased, with increased excretion of dextrose; it was decreased again on the ninth and tenth days to 169 Gm. of available dextrose. Because of the lag in the excretion of urinary dextrose, sugar continued to be excreted in gradually diminishing amounts to the twelfth day. In calculating the dextrose tolerance (table 4) by averaging the tolerance from the fifth to the twelfth day inclusive, we obtained an average tolerance of 176 Gm. Had this period of feeding the basal diet been extended sev-

TABLE 4.—*Period of Basal Diet; Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	5	6	7	8	9	10	11	12
Intake	155	180	213	240	201	169	169	169
Outgo	0	0.5	5	29.5	22.7	14.2	8.7	7
Tolerance	155	179	208	210	178	155	160	162
						Average Tolerance....		176

TABLE 5.—*First Artichoke Period; Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	13	14	15	16	17	18	19	20
Intake	199	188	188	169	169	169	169	169
Output	17	14	15	19	14	8	7	5
Tolerance	182	174	173	150	155	161	162	164
						Average Tolerance....		165

TABLE 6.—*Second Artichoke Period; Carbohydrate Intake, Outgo and Tolerance in Grams*

Day	21	22	23	24	25	26	27	28	29	30
Intake	175	184	192	192	191	169	169	169	169	169
Output	3.5	0	0	3.5	8.5	6	7	5	5	5
Tolerance...	172	184	192	188	183	163	162	164	164	164
							Average Tolerance....			174

eral more days, with a gradually diminishing output of dextrose, the tolerance would have been lowered by 4 or 5 Gm.

First Artichoke Period.—On the thirteenth day, an addition of dried artichokes (given with water), equivalent to 30 Gm. of levulose, was added to the patient's diet, and on the fourteenth and fifteenth days 19 Gm. The subject was then returned to the basal diet until the twenty-first day (table 5). At the first part of this period his tolerance was apparently higher than 176, but gradually decreased. This again is due to the lag in excretion of unused dextrose. The average dextrose tolerance for this period is 165 Gm. From this data, it is obviously impossible to show any increased tolerance to dried artichokes.

Second Artichoke Period.—A second series of observations were made from the twenty-first to the thirtieth day, during which time the

subject was fed 19 Gm. of artichoke powder on the twenty-first, 19 Gm. on the twenty-second and 22 Gm. on the twenty-third, on the twenty-fourth and on the twenty-fifth (table 6). Again the characteristic lag in the excretion of dextrose was seen. That is, at the first of the period even when the patient is fed at a higher level than his tolerance, there is no excretion of dextrose for several days, while after the excretion of dextrose is started, the excretion lasts for several days after the subject ceases to take greater amounts of carbohydrate than he can tolerate. The tolerance during this period was 174 Gm., which checks with the tolerance of the basal diet period (176 Gm.). Again these data do not show an increased tolerance due to the artichokes. An average of the two determinations for tolerance during the periods the artichokes were fed was 170 Gm., which is slightly less than the tolerance to the basal diet alone (176 Gm.). In any case, there is no evidence that dried artichokes are tolerated better than ordinary starch.

SUMMARY

A diabetic subject on a measured diet gave an average tolerance of 176 Gm. of dextrose daily. On the addition of powdered dried artichokes and over a period of eighteen days, the average tolerance was 170 Gm. No increased tolerance due to the addition of artichokes is evident, and we conclude that this form of carbohydrate is not tolerated in any greater quantities than starch. The difference in tolerance of 6 Gm. between the artichoke period and the basal diet period is within the limits of experimental error for this type of experiment. The average daily tolerance for the entire thirty days of the experiment is 172 Gm. The long lag in the excretion of dextrose is caused by the fact that the available dextrose of the basal diet (169 Gm.) is so close to the average calculated tolerance of the patient (172 Gm.). The p_H of the feces was not appreciably changed by the addition of carbohydrate in the form of dried powdered artichokes. We conclude that dried powdered artichokes have no advantage as a diabetic food.

THE CEREBROSPINAL FLUID IN MYXEDEMA*

WILLARD OWEN THOMPSON, M.D.
Fellow of the National Research Council and Research Fellow in Medicine, Harvard Medical School and Massachusetts General Hospital
PHEBE K. THOMPSON, M.D.
Research Fellow in Medicine, Massachusetts General Hospital
ESTHER SILVEUS, A.B.
AND
MARY ELIZABETH DAILEY, A.B.
BOSTON

Observations were made on the cerebrospinal fluid [1] of patients with myxedema before and after the administration of desiccated thyroid. These observations are presented under three headings: (1) the protein content, (2) the distribution of chloride ions between the plasma and the cerebrospinal fluid and (3) the rate of flow.

THE PROTEIN CONTENT

The measurements,[2] which are summarized in table 1, show two facts: 1. In thirteen of seventeen cases, the protein concentration was high during the period of myxedema.[3] Qualitative tests (the ammonium sulphate ring test of Ross and Jones, and precipitation with an equal quantity of 95 per cent alcohol) indicated that this was true for both albumin and globulin fractions. 2. In all but two cases a well marked drop in the concentration occurred as the basal metabolism approached normal, following the administration of desiccated thyroid. Data on a typical case are plotted in chart 1. In the two cases that showed no decrease, the protein content was normal to begin with.

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* From the Metabolism and Neurological Laboratories of the Massachusetts General Hospital.

1. The fluid was always removed under "basal conditions."

2. The method of Denis and Ayer (A Method for the Quantitative Determination of Protein in Spinal Fluid, Arch. Int. Med. **26**:436 [Oct.] 1920) was used. This is the best quantitative method known, the error being not greater than 5 per cent.

3. In a few of the cases showing the higher protein concentrations, there was some precipitation in the first six or seven tubes used in the colloidal gold reaction. The precipitation was usually most marked in the "tabetic zone." The reaction usually became normal following the administration of desiccated thyroid.

Qualitative tests usually showed a decrease in the concentration of both protein fractions, to the point where no precipitate could be seen.

The change persisted as long as the basal metabolism was held at a normal level by the administration of thyroid, but the concentration of protein tended to return to its previous high level when the administration was stopped (chart 1).

Two observations indicated that the protein content of cerebral fluid was also greater than normal: I. The protein concentration of the fluid obtained after withdrawing large quantities (from 60 to

TABLE 1.—*Effect of the Administration of Desiccated Thyroid on the Concentration of Protein and the Basal Metabolic Rate* *

				Before Administration of Thyroid						During Administration of Thyroid					
					Spinal Fluid						Spinal Fluid				
Case	Age	Sex	Laboratory Number	Basal Metbolic Rate, per Cent Normal	Concentration of Protein, Mg. per 100 Cc.	Globulin (Qualitative Test)	Albumin (Qualitative Test)	Cells per C.Mm. White	Cells per C.Mm. Red	Basal Metbolic Rate, per Cent Normal	Concentration of Protein, Mg. per 100 Cc.	Globulin (Qualitative Test)	Albumin (Qualitative Test)	Cells per C.Mm. White	Cells per C.Mm. Red
1 J. G.	53	♂	4236	—26	221	+	++	2	0-3	— 3	49	0	0	2	0
2 J. W.	50	♂	4224	—21	129	+	++	3	6	+ 2	58	+	+	4	0
3 H. L.	21	♂	4302	—34	111	+	+	0	1	+19	30	+	..	1	0
4 M. V. L.	47	♀	3984	—17	93	+	+	2	0	+23	32	0	0	..	..
5 M. B.	30	♀	4533	—40	80	+	+	1	0	—12	43	+	+	1	0
6 L. C.	53	♀	4532	—46	73	+	+	3	0	—10	32	0	0	2	0
7 E. G.	48	♀	4671	—43	72	+	..	2	0	— 9	36	..	..	1	0
8 E. McD.	43	♀	4423	—24	72	+	+	2	0-70	± 0	44	0	0	1	0
9 G. M.	33	♀	4434	—27	65	+	+	3	0	+ 7	27	0	..	1	0
10 A. J.	33	♀	4681	—28	61	+	+	2	0	—11	34	0	0	2	0
11 M. LeB.	43	♀	3532	—24	58	Sl.+	+	2	0	+15	41	+	+	0	0
12 M. B.	57	♀	1836	—24	48	Sl.+	0	1	0	— 5	24	0	0	1	0
13 A. H.	48	♀	1807	—22	46	+	+	2	0	+16	27	0	0	2	0
14 M. H.	35	♀	4179	—28	38	..	..	0	0	+ 8	44	..	..	3	0 to 1
15 D. B.	51	♀	4339	—25	34	Sl.+	?+	2	0	+17	21	0	0	0	8
16 M. M.	53	♀	4651	—29	34	0 to Sl.+	0	1	0-222	+ 6	22	0	0	2	0
17 J. W.	47	♀	2680	—22	28	0	0	2	3	± 0	31	0	0	0	0

* In most of the cases, each figure represents the average of two or more determinations made on different days. The determination of the protein content was usually made on the first 5 cc. of fluid removed from the lumbar region. Part of this table was published in the Journal of Clinical Investigation **6**: 251, 1928.

90 cc.) from the lumbar region was much greater than is found normally under these conditions. 2. In case 1, a cistern puncture was performed, and the protein content of the fluid obtained was high (130 mg. per hundred cubic centimeters). These facts suggest that in myxedema fluid of a high protein content may be filtered through the choroid plexus.

A high concentration of protein in cerebrospinal fluid is found in so many conditions that in itself it is of little diagnostic significance. It is worthy of note, however, that for several months, because of the presence of headaches and ataxia, there was some uncertainty as to whether J. G. (case 1) had myxedema or a tumor of the brain. The latter diagnosis was seemingly corroborated by the finding of a high

pressure as well as a high concentration of protein in the cerebrospinal fluid. The appearance of the patient was not characteristic of the full-blown picture of myxedema. The administration of desiccated thyroid, however, produced a well marked reduction in the concentration of protein, as well as a clinical cure.

Chronic nephritis is, of course, the disease most commonly confused with myxedema. It is of interest that in both diseases one may find albuminuria, a high blood pressure and a high concentration of protein [4] in the cerebrospinal fluid.

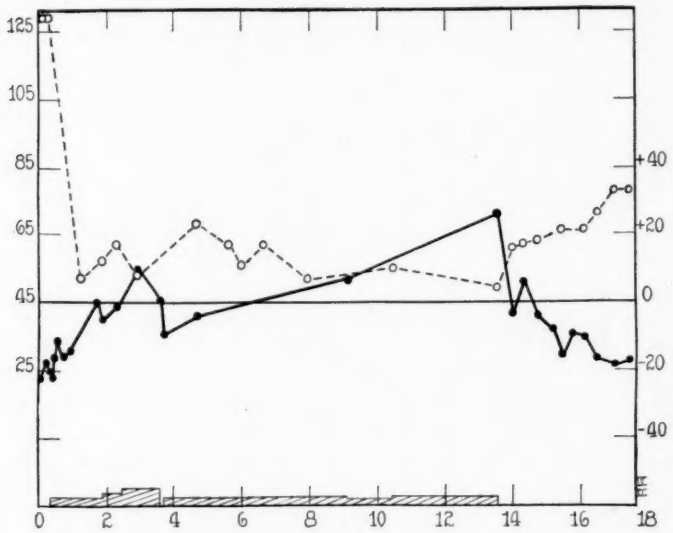

Chart 1.—A decrease in the concentration of protein in the cerebrospinal fluid and an increase in the basal metabolic rate following the administration of desiccated thyroid (case 2). The reverse changes occurred when the administration was stopped. The broken line represents the concentration of protein in the cerebrospinal fluid, measured in milligrams per hundred cubic centimeters along the vertical scale at the left. The solid line represents the basal metabolic rate, the percentage being shown by the vertical scale at the right; at the bottom of this scale, the Roman numerals represent grains of desiccated thyroid. The figures along the base of the chart indicate months.

The cause of the high protein content of the cerebrospinal fluid in myxedema is uncertain. A few observations already made [5] indicate

4. Lyttle, J. D.; Rosenberg, L., and Hearn, J. E.: Cerebrospinal Fluid in Nephritis, Arch. Int. Med. **39**:808 (June) 1927.

5. Thompson, W. O., and Alexander, B.: The Protein Content of the Cerebrospinal Fluid in Exophthalmic Goiter, Arch. Int. Med., to be published.

that in exophthalmic goiter the concentration is low and increases following a subtotal thyroidectomy. These observations are possibly related in some way to the increase in deposit protein in myxedema [6] and its depletion in exophthalmic goiter.[7] The albuminuria frequently present in myxedema usually disappears or decreases markedly when thyroid is administered. The high concentration of protein in the cerebrospinal fluid and the albuminuria may be, in part, manifestations of the same pathologic condition, namely, an altered permeability of the capillary membranes throughout the body.

TABLE 2.—*The Concentration of Chloride in Plasma and Spinal Fluid Before and During the Administration of Desiccated Thyroid (Case 16)*

		Plasma					
				Chloride as Sodium Chloride			
Date	Basal Metabolic Rate, per Cent Normal	Protein, Gm. per 100 Cc.	Water,* Gm. per 100 Cc.	Mg. per 100 Cc.	Mg. per 100 Cc. Plasma Water	Spinal Fluid Chloride as Sodium Chloride, Mg. per 100 Cc.	Ratio of Spinal Fluid Chloride to Plasma Chloride
Before Administration of Thyroid							
4/21/27	—30	7.0	93.50	583	624	717	114.9
4/26/27	—28	7.1	93.59	590	630	725	115.1
5/ 9/27	—23	6.8	93.40	601	643	739	113.5
5/13/27	—30	7.2	93.33	595	638	732	114.8
5/17/27	—27	7.5	93.09	588	632	726	114.9
5/20/27	—35	7.6	93.25	586	628	723	115.1
Average							114.7
During Administration of Thyroid							
6/13/27	+ 2	6.4	94.00	629	669	748	111.9
6/21/27	+ 6	6.1	94.25	638	677	758	112.0
6/28/27	+ 5	6.1	94.33	630	668	746	111.7
Average							111.9

* The concentration of water was determined by drying a known amount of plasma to a constant weight. It was assumed arbitrarily that the specific gravity of plasma was 1.028 before, and 1.026 during the administration of desiccated thyroid.

DISTRIBUTION OF CHLORIDE IONS

The ratio of the concentration of the chloride of the cerebrospinal fluid to that of the plasma is often less after the administration of desiccated thyroid. Data on a typical case are recorded in table 2. This decrease in the ratio is associated with an increase in the total volume of plasma and in the concentration of plasma water, and with a diminution in the concentration of protein in plasma. The obser-

6. Magnus-Levy, A.: Metabolism in Diseases of the Ductless Glands, in Noorden, C. von: Metabolism and Practical Medicine, Chicago, W. T. Keener and Company, 1907, vol. 3, p. 983. Boothby, W. M.; Sandiford, I.; Sandiford, K., and Slosse, J.: The Effect of Thyroxin on the Respiratory and Nitrogenous Metabolism of Normal and Myxedematous Subjects, Tr. A. Am. Phys. **40**:195, 1925.

7. Magnus-Levy (footnote 6, first reference).

vation is in harmony with numerous observations made by Fremont-Smith and Dailey,[8] which suggest that there is a relation between variations in the ratio of the chloride content of the spinal fluid to that of the plasma and variations in the concentration of protein in plasma.

RATE OF FLOW

With the patient in the horizontal lateral position, a lumbar puncture was performed in the usual manner. All readily available fluid was slowly drained off until the pressure was zero, and the rate of flow about uniform. All fluid that flowed from the needle was then collected for an hour. This was done frequently on three patients, both

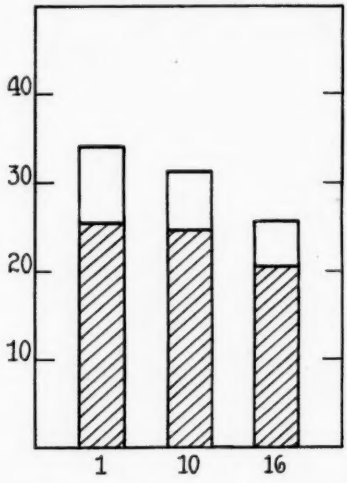

Chart 2.—The average rate of flow of the cerebrospinal fluid before (cross hatched areas) and after (total height of columns) the administration of desiccated thyroid. The vertical scale at the left shows the number of cubic centimeters of spinal fluid obtained. The case number appears below its respective column.

before and after the administration of desiccated thyroid. The average figures for each case under both conditions are plotted in chart 2. Owing to the crudeness of the method, we do not feel justified in concluding that the recorded increase in flow after the administration of thyroid is the result of an increased rate of formation. We feel, however, that the experiments indicate that the administration of thyroid

8. Fremont-Smith, F., and Dailey, M. E.: Unpublished data, referred to by Fremont-Smith, F.: The Nature of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927.

does not decrease the rate of formation of cerebrospinal fluid, as Frazier and Peet [9] claimed.

SUMMARY AND CONCLUSIONS

1. The concentration of protein in cerebrospinal fluid (lumbar) is high in most cases of myxedema and usually drops to within normal limits following the administration of desiccated thyroid.

2. The concentration of protein in cerebral fluid also appears to be high, although less than that in lumbar fluid.

3. Owing to the high concentration of protein in the cerebrospinal fluid, myxedema may, in rare instances, be confused with tumor of the brain.

4. The ratio of the chloride content of the spinal fluid to that of plasma is often less after the administration of desiccated thyroid.

5. The rate of flow of cerebrospinal fluid is not less, and may be greater after the administration of thyroid.

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9. Frazier, C. H., and Peet, M. M.: The Action of Glandular Extracts on the Secretion of Cerebro-Spinal Fluid, Am. J. Physiol. **36**:464, 1914-1915.

THE DIURETIC ACTION OF THE PARATHYROID EXTRACT *

W. C. HUEPER, M.D.
CHICAGO

The literature of recent years contains several reports concerning the diuretic effect of parathyroid hormone (Mason,[1] Meakins,[2] Hueper,[3] McCann [4]). As the mechanism of this action is not known, the report of some observations made on the kidneys of dogs given injections with parathyroid extract-Collip may be of interest.

Sympathicotonic spastic contractions of the vasa afferentia of the glomeruli are considered by Volhard [5] and Jungmann [6] as the cause of oliguria and anuria in glomerulonephritis and reflex anuria. This conception has found practical expression in several methods used in the therapeutic management of these conditions as the anesthesia of the splanchnic nerves after Kappis (Neuwirt [6]), general anesthesia to lessen the splanchnic tonus, parenteral injection of blood and protein substances to bring about a change in the tonus of the vegetative nervous system, denervation of the pedicle of the kidney to cause an interruption of the renal nervous supply, especially that by the splanchnic nerve, decapsulation of the kidney to relieve the capsular pressure and to produce simultaneously a partial denervation of the kidney, a procedure warmly recommended by Volhard.

During the course of experiments with dogs receiving injections of parathyroid extract, I made the observation that this hormone has a strong vagotonic effect, evidenced by a decrease of the pulse rate, prolongation of the systole, shortening of the diastole, hyperemia of the vessels of the abdominal organs, and intensification of the peristalsis of

* Submitted for publication, May 24, 1929.

* From the Department of Pathology, Loyola University School of Medicine and Laboratories of Mercy Hospital.

1. Mason, E. H.: A Case of Chronic Nephritis Treated with Collip's Parathyroid Extract, Canada M. A. J. **16**:538, 1926.

2. Meakins, J. C.: Reaction of Chronic Nephrosis to Thyroid and Parathyroid Medication, J. A. M. A. **89**:149 (July 9) 1927.

3. Hueper, W.: Metastatic Calcifications in the Organs of the Dog After Injections of Parathyroid Extract, Arch. Path. **3**:14 (Jan.) 1927.

4. McCann, W. S.: Diuretic Action of Parathyroid Extract-Collip in Certain Edematous Patients, J. A. M. A. **90**:249 (Jan. 28) 1928.

5. Volhard, F.: Ueber die Behandlung der Nierankrankheiten, Ztschr. f. Urol. **19**:5, 1925.

6. Jungmann, P.: Die Pathogenese der Anurie und die Grundlagen ihrer Behandlung, Klin. Wchnschr. **6**:241, 1927.

the stomach and intestine. When the amount of the injected parathyroid extract was adjusted in such a way that the blood calcium level was raised to about 15 mg. in 100 cubic centimeters of blood, a markedly increased excretion of urine was noticed. Dogs killed during this stage, on histologic examination of the kidneys showed that the blood vessels, especially the glomerular capillaries, were extremely distended with blood. There were no other changes observed in the kidney, especially no tubular degenerations or calcium precipitations.

COMMENT

The conclusion may therefore be justified that the increased excretion of urine observed in these dogs was at least to some extent due to the active hyperemia of the renal vessels caused by the increased vagotonus resulting from the injections of the parathyroid extract. As injections of parathyroid extract are not dangerous to the patient if the blood calcium level is properly controlled, this method may be tried for relief from oliguria and anuria before more radical and dangerous measures are used. It may be noted furthermore that the increase of the calcium level in the blood which is frequently found to be lowered in glomerulonephritis will have a beneficial effect on the often concomitant hypertension and will help to regulate favorably the heart action. Medication with parathyroid extract may represent a causative treatment in reflex anuria, but is of only symptomatic value in the therapeutic management of glomerulonephritis.

OPIUM ADDICTION

VIII. THE EFFECTS OF INTRAMUSCULAR AND INTRAVENOUS ADMINISTRATION OF LARGE DOSES OF MORPHINE TO HUMAN ADDICTS *

ARTHUR B. LIGHT, M.D.
AND
EDWARD G. TORRANCE, M.D.
PHILADELPHIA

Wide variations in the quantity of the drug used and also in the frequency of administration to prevent withdrawal symptoms are encountered among different human addicts as well as in the same addict at various periods during addiction. This variation is found not only in dosage and frequency of administration, but also in the methods of administration. The choice as to the latter in 95 per cent of our cases was the hypodermic method, but sniffing of heroin, oral administration, pipe smoking of opium and intravenous administration were also encountered. With these variations in mind we administered additional amounts, both intramuscularly and intravenously, in order to determine, first, what physiologic effects are brought about in human addicts by quantities greater than those required to prevent withdrawal symptoms; second, whether abrupt withdrawal for a period of forty-eight hours decreases the intravenous tolerance of the addict, and third whether these additional amounts prolong the period of comfort on the part of the addict.

Samples of blood were analyzed for morphine by Dr. A. K. Balls [1] of the Department of Pharmacology, University of Pennsylvania, immediately following the completion of the injection.

EXPERIMENTAL PROCEDURE

Five addicts, one of whom was at times accustomed to the intravenous administration of the drug, while the other four used the hypo-

* Submitted for publication, March 5, 1929.

* From the Narcotic Wards of the Philadelphia General Hospital.

* Expenses of this committee were defrayed by the Committee on Drug Addictions, New York City, and were carried out under the guidance of the Philadelphia Committee for the Clinical Study of Opium Addiction in the Narcotic Wards of the Philadelphia General Hospital which were placed at our disposal through the courtesy of the Director of Public Health, City of Philadelphia.

1. Balls, A. K., and Wolff, W. A.: The Determination of Morphine, J. Biol. Chem. **80**:379 (Dec.) 1928.

dermic method, volunteered as subjects for the experiments planned. All of the experiments, whether the drug was given intramuscularly or intravenously, were made while the patients were reclining in bed for at least half an hour without having had breakfast. Except in the cases in which morphine was withheld for a period of forty-eight hours, the regular dosage was given intramuscularly, usually about 8:30 a. m.

The morphine sulphate solution used in these experiments was especially prepared by the department of pharmacology of the University of Pennsylvania in an isotonic solution of sodium chloride, 5 cc. containing 2 grains (0.13 Gm.) of morphine sulphate. When the drug was given intramuscularly, the point of injection was usually over the anterior part of the chest or in such areas as appeared to be free from recent injections. The intravenous administration was always given into the median basilic vein. In all cases of intravenous administration, 2 grains was given at each injection, except in one case following a period of withdrawal for forty-eight hours, when at the close of the experiment the dosage for several injections was raised to 4 grains (0.26 Gm.).

The observer who administered the drug reported the general behavior and color of the skin of the subject, as well as any remarks on his part. Another observer confined his attention to the blood pressure, a third to the counting of the pulse and a fourth to the respirations. The figures for blood pressure are the average for as many as could be accurately taken in a five minute period. The figures for pulse rate and respirations are the averages of a five minute count. In the protocols of two experiments given in this paper are found the actual figures and the remarks made by the addict during the entire period of administration. Samples of blood for the analyses reported were taken just before the administration of the drug was begun and, as a rule, about fifteen or twenty minutes following the last dosage. In four cases, electrocardiographic studies were made preceding the administration and immediately following the last dosage given.

The actual time required for each injection of 2 grains varied from one minute and twenty seconds to four minutes and twenty-two seconds, depending on the reaction of the patient.

RESULTS

Tables 1, 2 and 3 contain the data obtained from the various experiments. Chart 1 shows graphically the changes in blood pressure, respiration and pulse rate obtained in an experiment in which 30 grains (1.95 Gm.) of morphine sulphate was given intravenously to an addict over a period of two hours and twenty-four minutes, he having previously received his normal dosage of 17 grains (1.1 Gm.) in twenty-four hours. Protocols 1 and 2 give the actual determinations of blood pressure, pulse and respiratory rates during the intravenous administration

TABLE 1.—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intramuscularly to Human Opium Addicts*

Time and Case No.	Dosage of Drug, Grains	Blood Pressure	Respirations per Minute	Pulse per Minute	P-R Interval, Seconds	p_H of Blood	Sugar, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Dry Matter of Whole Blood
Case 26-35									
9:55 a. m.	..	104/61	10	55	0.155	7.33	90	11	20.40
9:57 a. m.	5	104/61							
11:11 a. m.	6								
11:53 a. m.	6								
Total	17								
12:00 noon		101/55	9	60	0.160	7.32	92	10	19.16
Case 26-85									
9:50 a. m.	..	90/68	8	66	0.156	7.40	80	12	20.23
9:56 a. m.	3								
10:56 a. m.	..	98/60	8	60					
11:14 a. m.	4								
11:52 a. m.	4								
Total	11								
12:29 p. m.		102/64	10	58	0.172	7.38	90	9	19.69
Case 26-39									
10:34 a. m.	..	116/68	14	60					
10:35 a. m.	5								
11:07 a. m.	..	108/62	13	59					
11:10 a. m.	5								
Total	10								
11:31 a. m.		106/64	14	60					

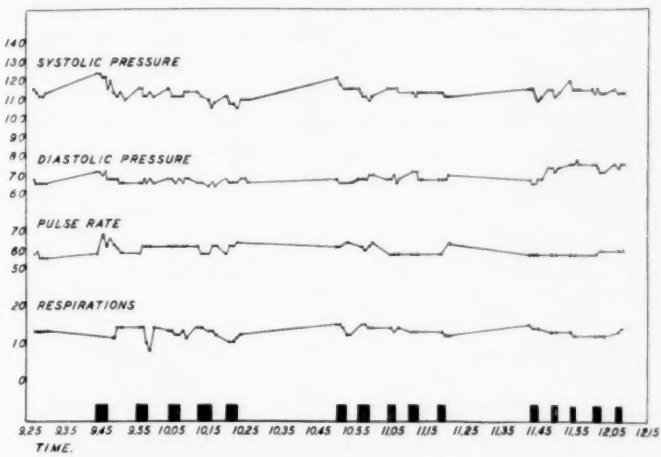
TABLE 2.—*The Effects of the Administration of Additional Amounts of Morphine Sulphate Intravenously to Human Opium Addicts*

Case No.	Pulse	Respirations	Blood Pressure	P-R Interval, Seconds	Hemoglobin	Dry Matter of Whole Blood	Oxygen Content of Venous Blood	Percentage Saturation of Oxygen of Venous Blood	p_H of Blood
26-21									
Before injection	85	22	126/68	0.176	14.9	20.83	9.3	62.4	7.45
After injection	68	18	118/76	0.184	14.4	20.27	11.3	78.5	7.41
14 grains, 2 hours*									
26-39									
Before injection	60	14	115/68	0.160					
After injection	62	14	116/68	0.160					
30 grains, 2 hours 23 minutes*									
26-56				Erythrocytes	Leukocytes				
Before injection	72	12	117/69	4,560,000	6,600				
After injection	73	11	122/70	4,640,000	5,800				
6 grains, 1 hour 37 minutes									

* Analysis of the blood for the presence of morphine sulphate by Dr. Balls (J. Biol. Chem. **80**: 379 [Dec.] 1928) of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg. per 25 cc. of blood, equivalent to approximately 4 grains in total blood.

of morphine sulphate to the same addict during his regular dosage and following a forty-eight hour period of withdrawal. The protocols also contain the remarks of the patient as well as such observations as were deemed important.

In the three cases in which the morphine was administered intramuscularly in dosages of six, four and three times the amount to which the addicts were accustomed, no significant changes in the pulse, respiration, blood pressure, P-R interval, blood reaction or blood content in dry matter, urea nitrogen or sugar could be found. In one case the blood pressure fell from 116 systolic, 68 diastolic to 106 systolic, 64 diastolic, but in another it rose from 90 systolic, 68 diastolic to 102 systolic, 64 diastolic; in the third, the change was within the error of reading.



Effect on pulse rate, blood pressure and respiration of 30 grains (1.95 Gm.) of morphine sulphate given intravenously to a human addict over a period of two hours and twenty-four minutes. The shaded areas indicate the time of injections, of 2 grains each.

When the drug was administered intravenously to three different patients in dosages of seven, nine and six times the usual quantity, there was no change in the pulse rate, respiration and blood pressure in two. Hemoglobin, the dry matter of the whole blood and the blood reaction showed no significant change in the one case in which analysis of the blood was made. In one addict given nine times the usual dose, the P-R interval remained the same, but in the subject given seven times the usual dosage it was prolonged from 0.176 to 0.184 second. In the latter case, however, the pulse rate dropped from 85 to 68 per minute, the blood pressure fell from 126 systolic, 68 diastolic to 118 systolic,

76 diastolic, and the respirations from 22 to 18 per minute. This patient (case 26-21) showed definite signs of fear before the injections were begun. As the injections proceeded and no untoward results were felt, whether because of the action of the drug or not, this addict showed less apprehension, which we believe to be the factor in these changes. The percentage of oxygen saturation of the venous blood taken from the same vein at the elbow rose from 62.4 to 78.5. A count of the red and white blood cells made in one case showed no change.

TABLE 3.—*The Effects of the Administration of Morphine Sulphate Intravenously Following a Forty-Eight Hour Withdrawal Period in Human Opium Addicts*

	Case 26-21		Case 26-39	
	At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate	Following Administration of the Morphine Sulphate, 11 Grains, in 1 Hour 16 Minutes	At the End of 48 Hours Withdrawal Before Administration of the Morphine Sulphate	Following Administration of the Morphine Sulphate, 20 Grains, in 53 Minutes*
Pulse	80	96	72	79
Respirations	21	18	11	11
Blood pressure	122/74	122/70	109/64	102/63
Erythrocytes	5,150,000	5,550,000	5,240,000	5,420,000
Leukocytes	10,800	12,200	13,300	12,700
Differential count:				
Polymorphonuclears	77	79	76	73
Lymphocytes	20	19	21	25
Transitionals	2	1	3	2
Basophils	1	0		
Large mononuclears	0	1		
Baskets	4	5		
Arneth:				
Old	68	61	68	67
New	32	39	32	33
Fragility:				
Complete	36	36	32	30
Partial	44	44	48	48
Coagulation	2 min.	1 min. 50 sec.	2 min.	1 min. 40 sec.
pH	7.44	7.39		
Carbon dioxide capacity	54	56		
Hemoglobin	16.1	16.9		
Percentage of saturation of oxygen of venous blood	61.7	84.1		
Dry matter of whole blood	22.22	22.59		
Dry matter of plasma	9.59	9.64		

* Analysis of the blood for the presence of morphine sulphate by Dr. Balls of the Department of Pharmacology, University of Pennsylvania, resulted in the finding of less than 1 mg. per 25 cc. of blood.

The two cases studied during the intravenous injection of morphine sulphate following a withdrawal period of forty-eight hours both showed rises in the pulse rate and a slight fall in the pressure. Respirations decreased slightly in one and remained the same in the other. There was a rise in the number of red blood cells of 400,000 per cubic millimeter in the one case and of 180,000 in the other. The white blood cell count per cubic millimeter of blood fell slightly in one and rose correspondingly in the other.

The differential counts, Arneth counts and the fragility of the cells as well as the coagulation time remained practically the same. In one case, the dry matter of the whole blood rose slightly as did the hemo-

globin, but the dry matter of the plasma remained the same. The blood p_H fell from 7.44 to 7.39; the carbon dioxide capacity remained the same. There was a rise of from 61.7 to 84.1 in the percentage of oxygen saturation of venous blood drawn from the vein.

The behavior of the addicts following the large doses given both intravenously and intramuscularly is of considerable interest. In the three cases studied following intramuscular injection, it was impossible to detect any change in appearance. One addict stated that he felt "loaded"; the other two expressed their feelings as being unchanged during the injections. There was no evidence of drowsiness. Interest was shown in the surroundings, and an occasional cigaret was smoked. One subject read the newspaper when observations were not being taken. All three requested their usual dosage at the next regular interval and ate their regular meals.

Two of the three addicts who acted as the subjects for intravenous injections of morphine during regular administration served also as the subjects for the intravenous administration following a forty-eight hour withdrawal period. The patient in case 26-39 had occasionally used the intravenous method of administration during addiction outside the ward but while in the ward was given the drug hypodermically.

During the intravenous administration of the drug during the period of regular dosages, the patients in cases 26-21 and 26-56 complained at times of itching and severe tingling in the extremities, back of the neck and face, as well as over the anterior part of the chest, which would last for a minute or two while the drug actually was being injected. At one time during the injection, the addict in case 26-21 complained bitterly of a pain in his head as if he "were hit in the head with a baseball bat" and again, as he expressed it, "as if someone were jabbing his knuckles in the back of my head." Yet a few minutes later he would state that he felt fine and was as well as if he had never taken drugs in his life. At the time that the patients stated that they experienced these sensations, no changes could be noticed by the observers in the pulse rate, respiration and blood pressure, although there appeared to be an increased redness of the face, neck and anterior part of the chest. On the other hand, the addict in case 26-39 who received by far the largest doses during the intravenous administration scarcely felt any of the sensations described by the other two. It is true that he had at times been accustomed to intravenous administration, and he said that he was familiar with these sensations but that he felt them only slightly and not enough to annoy him.

Protocol 2 gives in detail the observations and remarks of patient 26-39 during the intravenous administration following the forty-eight hour withdrawal period. They need no comment, except again to call attention to the fact that during the last dose of 4 grains the subject

requested a hpodermic injection into the muscle. The experiment was finished at 11:05 a. m., at which time he was given 3 grains hypodermically. At 3 p. m., he requested another hypodermic injection of 3 grains. Between these two intervals, he was about the ward as usual, read a newspaper and ate a hearty lunch.

The reaction of patient 26-21 who received 11 grains intravenously in one hour and sixteen minutes following a forty-eight hour withdrawal period was similar to that in patient 26-39. He was considerably more nervous than patient 26-39. The violent twitching of the labial muscles present before the injections were begun became considerably less evident only after the seventh grain was injected, at an interval of one hour and six minutes after the injection of the first two grains. These twitchings were still slightly present after the last dosage of a total of 11 grains. This patient complained at times of feeling on fire and of "that awful tingling in the body." However, careful observations of blood pressure and pulse and respiration rates again showed no marked changes during these complaints. His face and neck and the anterior part of the upper half of the chest also showed the brilliant red color found in case 26-39, and he scratched this area at frequent intervals. At the end of the experiment he complained of feeling drowsy, but he immediately got up from the bed, started conversing with several other addicts and ate his regular lunch. He slept for a short interval following his lunch, but at 4 p. m. requested his usual dosage of 2 grains of morphine hypodermically.

PROTOCOLS

PROTOCOL 1 (case 26-39).—*The Intravenous Administration of 30 Grains (1.9 Gm.) of Morphine Sulphate in Two Hours and Twenty-Four Minutes.*

This subject, aged 29, had been addicted to the use of the drug for 13 years (?). He was 5 feet 10½ inches (179 cm.) tall and weighed 220 pounds (99.7 Kg.) He had received a dosage of morphine sulphate of from 21 to 25 grains (1.36 to 1.62 Gm.) per twenty-four hours in the ward for the last five days. On the day of the experiment, Feb. 14, 1927, the patient did not receive breakfast.

8:30 a. m.: Morphine sulphate, 4 grains (0.26 Gm.) given hypodermically.
8:45 a. m.: Patient reclining in bed.

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9:26 a. m.				
9:27.15 seconds	118/70	14	60	
9:27.55 seconds	116/68	14	61	No comment on part of patient.
9:28.37 seconds	114/68	14	58	
9:29.25 seconds	114/68	14	58	
9:30.10 seconds	116/68	14	58	
9:44 a. m. Intravenous injection of 2 grains (0.13 Gm.) morphine sulphate begun.				
9:44.22 seconds	126/74		60	

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9:45.08 seconds	126/74			
9:45.10 seconds				Felt a little tingling sensation. "I have not got the kick yet."
9:45.46 seconds	124/72		70	
9:46.25 seconds	124/74			
9:46.36 seconds				Did not feel anything.
9:47.01 seconds	118/70		64	
9:47.49 seconds	122/70		68	
	Injection finished.			
9:49.07 seconds	116/70	12	65	
9:50.12 seconds	114/70	15	63	
9:51.07 seconds	116/68	15	61	
9:51.49 seconds	112/68			Patient did not feel the slightest thing. "No kick at all."
9:55 a. m.:	Second dosage of 2 grains of morphine sulphate, intravenously, begun.			
9:56.09 seconds	118/68	15	60	
9:56.46 seconds	118/68			
9:57.29 seconds	114/70	15	64	
9:58.24 seconds	114/68	11	64	
	Injection finished.			Patient dozed.
9:59.26 seconds	116/70	9	64	"How do you feel?" "Just flushing up a little, that's all."
10:00.37 seconds	114/68	15		
10:04 a. m.:	Third dosage of 2 grains of morphine sulphate, intravenously, begun.			
10:04.49 seconds	118/70	14	64	
10:05.34 seconds	114/70	14	64	
10:06.25 seconds	114/68	13	64	
10:07.16 seconds	114/70	13		
	Injection finished.			
10:08.11 seconds	114/68	14	64	Patient denied any feeling of tingling or flushing up. "I do not feel any different, just the same."
10:08.54 seconds	116/70			
10:09.47 seconds	116/70	12	64	
10:12 a. m.:	Fourth dosage of 2 grains of morphine sulphate, intravenously, begun.			
10:12.56 seconds	116/68	15	64	
10:13.58 seconds	114/68	15	60	
10:15.02 seconds	112/66	14	60	
10:15.54 seconds	108/68	14	64	
	Injection finished.			Patient still said, "I feel all right."

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10:16.55 seconds	110/66	13	64	
10:20 a. m.: Fifth dosage of 2 grains of morphine sulphate, intravenously, begun.				
before start	114/70	11	60	
10:21.26 seconds	110/68	11	64	
10:22.15 seconds	110/68	12	64	
10:23.24 seconds	108/68	13	66	
Injection finished.				
10:24.06 seconds	112/70			
10:25.00 seconds	112/70			Patient felt drowsy; dozed just sitting up in chair smoking. Said he was not hungry.
10:25.48 seconds	112/68			
10:30 a. m.: Blood drawn.				
10:50 a. m.: Sixth dosage of 2 grains of morphine sulphate, intravenously, begun.				
10:50.39 seconds	124/70	16	64	
10:51.30 seconds	120/68	16	64	
10:52.15 seconds	118/68	15		
10:53.01 seconds	118/68			
Injection finished.				Patient still denied any sensations. "I feel all right."
10:53.42 seconds	118/68	13	66	
10:54.30 seconds	118/68	13		
10:56 a. m.: Seventh dosage of 2 grains of morphine sulphate, intravenously, begun.				
10:56.04 seconds	118/70			
10:56.44 seconds	116/68			
10:57.31 seconds	114/70	16	64	
10:58.16 seconds	114/70	16	62	
10:59.02 seconds	112/72	15	64	"I feel all right. No, I have not felt any tingling."
Injection finished.				
10:59.53 seconds	114/72	15	66	
11:04 a. m.: Eighth dosage of 2 grains of morphine sulphate, intravenously, begun.				
before start	118/70			
11:04.40 seconds	118/70			
11:05.40 seconds	118/72	15	60	
11:06.23 seconds	118/68	14	60	
11:07.03 seconds	Injections finished.			
11:07.08 seconds	116/70	15	60	"I feel all right."
11:10 a. m.: Ninth dosage of 2 grains of morphine sulphate, intravenously, begun.				
11:10.41 seconds	116/74			
11:11.16 seconds	112/74	14	60	

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
11 : 12.01 seconds	116/70			"That's the time I felt it." Itching around face and at back of neck.
11 : 12.58 seconds	116/70	14	60	
11 : 13.59 seconds	Injection finished.			
	Patient lay on the bed most of the time with his eyes closed. Looked peaceful enough. Was not much interested in the actions going on around him. "What am I thinking about?" "Oh, nothing, just resting. Just thinking of things in general, nothing in particular. I am perfectly satisfied. I am thinking of what I am going to eat." "Oh, no, I do not think I could stay this way the rest of my life."			
11 : 18 a. m.:	Tenth dosage of 2 grains of morphine sulphate, intravenously, begun.			
11 : 18.52 seconds	116/70			
11 : 19.35 seconds	116/70	14	60	
11 : 20.15 seconds	114/70	13		
11 : 20.54 seconds	Injection finished.			
11 : 21.04 seconds	114/72	13	66	
11 : 22 a. m.:	Blood drawn.			
11 : 43 a. m.:	Eleventh dosage of 2 grains of morphine sulphate, intravenously, begun.			
11 : 43.22 seconds	118/70			
11 : 43.56 seconds	118/68	16	60	
11 : 44.40 seconds	114/68	15	60	
11 : 45.25 seconds	112/70	15	60	Patient said he felt the "pins and needles" slightly that time.
11 : 46.04 seconds	Injection finished.			
11 : 46.10 seconds	114/70			
11 : 48 a. m.:	Twelfth dosage of 2 grains of morphine sulphate, intravenously, begun.			
11 : 48.12 seconds	118/76	14	60	
11 : 49.01 seconds	118/76	14	60	
11 : 49.57 seconds	114/74			
	Injection finished.			
11 : 50.30 seconds	116/76			
11 : 54 a. m.:	Thirteenth dosage of 2 grains of morphine sulphate, intravenously, begun.			
before start	122/78			
11 : 54.52 seconds	118/78	14	60	
11 : 55.42 seconds	118/80	13	60	
11 : 56.00 second	Injection finished.			"Outside of that little tingling sensation, I don't feel anything."
11 : 56.20 seconds	118/78			
12 : 00 noon:	Fourteenth dosage of 2 grains of morphine sulphate, intravenously, begun.			
before start	118/78			
12 : 00.46 seconds	116/78			
12 : 01.35 seconds	118/76	13	60	

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
12:02.22 seconds	116/74	13	62	
12:02.48 seconds	Injection finished.			
12:03.04 seconds	116/74	13		
12:06 p. m.:	Fifteenth dosage of 2 grains of morphine sulphate, intravenously, begun.			
12:06.42 seconds	118/78			
12:07.20 seconds	116/76	14	62	
12:07.52 seconds	116/78			
12:08.24 seconds	Injection finished.			
12:08.29 seconds	116/78	15	62	
12:45 p. m.:	Blood drawn.			
12:47 p. m.:	Electrocardiogram.			
	Twice during the experiment, the patient asked for and received a glass of water.			

PROTOCOL 2 (case 26-39).—*The Intravenous Administration of 20 Grains (1.3 Gm.) of Morphine Sulphate in a Period of Fifty-Six Minutes Following a Withdrawal Period of Forty-Eight Hours.*

This subject, aged 29, had been addicted to the use of the drug for years (?) He was 5 feet 10½ inches tall and weighed 216 pounds (98 Kg.). The daily dosage in the ward for the last twenty-three days has been from 21 to 25 grains of morphine sulphate per twenty-four hours; eighteen days previous to this experiment he received 30 grains of morphine sulphate intravenously in a period of two hours and fifty-three minutes. For the past forty-eight hours, the drug had been withheld.

At 9.27 a. m., the patient was reclining in bed. The visible signs of withdrawal were frequent yawning, lacrimation, dilated pupils, slight cough, difficulty in breathing through the nose, occasional tremor of the right leg and extreme nervousness manifesting itself mostly in begging for the experiment to begin. The subject appeared to be suffering with a severe cold. No rise in temperature occurred.

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9:32.25 seconds	110/64	11	75	Yawned.
9:33.01 seconds	110/66	12	74	
9:33.36 seconds	108/62	12	74	Yawned.
9:34.08 seconds	110/64	12	70	
9:34.47 seconds	110/64			
9.36 a. m.			72	Coughed.
9:38 a. m.				
9:38.40 seconds	110/64			
9:39.18 seconds	110/66	16	71	
9:40.05 seconds	110/64			Coughed.
9:40.35 seconds	110/64	16	75	
9:41.10 seconds	112/64			Yawned.
9:41.18 seconds		14	76	Coughed.
9:41.54 seconds	114/66			
9:42.35 seconds	112/64	16	73	
9:42.40 seconds				Coughed.
9:43.23 seconds	112/68	14	72	Yawned, moving feet.

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
9:44.05 seconds	112/68			Yawned, moving feet.
9:44 a. m.: Coughed and yawned.				
9:45 a. m.: Testing of reflexes of knees.				
9:49 a. m.: Blood drawn.				
9:52 a. m.: Yawned.				
9:58 a. m.: Patient rose up in bed in anticipation.				
10:00 a. m.: Yawned and said: "Give me the shot and a damp towel for the back of my neck, that's all." Yawned twice more.				
10:02 a. m.: How do you feel?" "I am aching all over and yawning. I feel sick at my stomach. There's nothing quiet about me. My nose feels stopped up. I could vomit. Gagging, that's what that cough is, but the minute you shoot it in the vein I will feel better."				
10:05 a. m.: First dosage of 2 grains of morphine sulphate, intraveneously, begun.				
10:05.12 seconds	116/68			
10:06.05 seconds	114/66	24	70	
10:06.12 seconds				"I feel it now—my nose is cleared up. No other sensation. My nose has stopped running. It dries right up."
10:07.01 seconds	116/64	12	72	No other sensations. No tingling or pain in back of neck. "You are going too slow."
10:07.13 seconds	Injection finished.			
10:07.45 seconds	110/66	12 11		
10:11 a. m.: Second dosage of 2 grains of morphine sulphate, intravenously, begun.				
before start	112/68			
10:11.15 seconds	114/66			
10:11.57 seconds	116/68			
10:12.12 seconds		12	72	"I can feel it now. Through the shoulders. Sort of pulls together. Your nerves get quiet. I feel warmer now."
10:12.28 seconds				"My cold has gone now. Eyes are not watering, but you do not get relieved, not yet. Twitches have not gone yet. Only in that right leg."
10:12.56 seconds	112/70	11	72	
	Injection finished.			
10:13.35 seconds	112/76	11	72	
10:16 a. m.: Third dosage of 4 grains of morphine sulphate, intravenously, begun.				
10:16.25 seconds	108/68			

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10:16.55 seconds	112/70	20	80	"My knees are beginning to relax."
10:17.23 seconds		12 (½ min.)		
10:17.30 seconds	112/68		80	
10:18.20 seconds	112/68			"Twitching of legs and knees. I have that twitchy feeling in just that right leg."
10:19.14 seconds				"Now I am just getting that 'weight' in my stomach."
10:19.20 seconds	108/70			"I am beginning to flush up. You don't get that pins and needles when you go so slow."
10:19.26 seconds			80	
10:20.26 seconds	110/68			
10:20.55 seconds				"Now I got that tinge that sort of makes your face and hands swell up."
	Injection finished.			
10:21.20 seconds	108/68			Patient's ears were extremely red but he said that they did not burn.
10:24 a. m.:	Fourth dosage of 4 grains of morphine sulphate, intravenously, begun.			
10:24.30 seconds	112/68			
10:25.25 seconds		13	62	Patient denied feeling
10:25.30 seconds				drowsy. "I feel better than I did, yes."
10:25.34 seconds	108/68			"Could I stand more? Sure, your nerves seem to eat it right up as soon as you get it."
10:26.15 seconds	110/68	12	84	
10:27.25 seconds		11	86	"I feel a little tingling in the back of my neck."
10:27.35 seconds	108/66			
	Injection finished.			
10:28.30 seconds	106/68	11	86	

Patient complained of severe itching and sat up in bed scratching himself violently on the face, which was flushed. He complained of that tingling sensation over this area.

A brilliant red flush was now noted over the face, neck and upper part of the chest anteriorly. This did not extend to the arms or the lower part of the chest and was not noted elsewhere. Patient complained of a terrific itching over the red area; this was especially marked at the back of the neck. He rubbed and scratched furiously for about five minutes and for the rest of the experiment the itching was present, but in a lesser degree.

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
10:43 a. m.: Reflexes of both knees and ankles were tested by Dr. Stanley Cobb of Boston, who expressed the opinion that they seemed active enough and appeared practically normal.				
10:48 a. m.: Fifth dosage of 4 grains of morphine sulphate, intravenously, begun.				
10:49.01 seconds	104/64		76	
10:49.43 seconds	102/64			
10:49.50 seconds				Patient lay with closed eyes and when asked about his thoughts said: "I was just thinking about McCarthy, another patient here, that's all."
10:50.21 seconds	102/62		78	
10:50.45 seconds				"How do you feel?" "All right. My nerves are all right. Yes, I could stand another shot."
10:50.55 seconds	102/64			
10:51.55 seconds	102/62		80	
Injection finished.				
10:52.55 seconds	102/64		78	
Patient scratched the palm of his right hand. He said he was hungry. "No, the weight in my stomach has gone. That lasted only a very few minutes. It was a depressed feeling down there, something heavy down there."				
10:58 a. m.: Sixth dosage of 4 grains of morphine sulphate, intravenously, begun.				
10:58.20 seconds	104/64			
10:59.02 seconds	102/64		76	
10:59.25 seconds				"I feel all right now and have for the last ten minutes. I would like a hypo in the muscle. I will wait for fifteen minutes though."
10:59.42 seconds	102/64			
11:00.15 seconds	104/66		80	
11:00.40 seconds				Felt kind of dry in the mouth. (He asked for a glass of water.) "My nose is all free and everything now. I am not coughing and my stomach is all right. Yes, I am comfortable now."
11:01.05 seconds	102/64			"No, I am not drowsy" (although patient spoke slowly). "Warm?" "Yes, but not too warm."

Time	Blood Pressure	Respiration	Pulse Rate	Remarks
11 : 01.59 seconds	102/64		80	
11 : 02.43 seconds	102/62			Felt a tingling in the jaws —just an itching back there, that was all.
	Injection finished.			
11 : 03.14 seconds	102/62		80	

Patient did not complain of a headache but said that he would like a hypodermic injection into the muscle because "you usually get one when you get it in the vein like this, and it goes so slow." He denied that he had a headache now, however.

COMMENT AND LITERATURE

We have demonstrated in the foregoing experiments that in the addicts who acted as subjects morphine was tolerated in far greater amounts than those required to prevent withdrawal symptoms. The intramuscular dosages were three, four and six times the amounts usually given, while the intravenous dosages were six, seven and nine times the usual quantities. In the two cases in which the regular dosage was abruptly withdrawn for a period of forty-eight hours, the tolerance for intravenous doses was still present, in one case 20 grains (1.3 Gm.) being administered in fifty-six minutes and in the other 11 grains (0.7 Gm.) in one hour and sixteen minutes. These additional quantities did not prolong the period before the addict again requested his drug. This is contrary to the statement of Bishop,[2] who claimed that additional quantities prolonged proportionately the interval between demands for the drug.

The physiologic changes brought about by these additional amounts taken as a whole may be regarded as practically negative. In case 26-21, there was an increase in the venous oxygen of the blood drawn from the median basilic vein following administration of these large quantities compared to that present while the addict was receiving his regular dosage and also following the abrupt withdrawal period. All the intravenous experiments were accompanied by a distinct flushing of the face, neck and upper part of the chest anteriorly. All the addicts complained of feeling more or less warm, as well as "loaded." Careful studies of the blood pressure and pulse rates did not reveal any essential differences accompanying the sensations described by the addict.

The question naturally follows, "What has become of this additional morphine and why has it been ineffective in producing any pronounced physiologic changes? Failure of absorption cannot be considered, as in

2. Bishop, Ernest S.: The Narcotic Drug Problem, New York, The Macmillan Company, 1921, p. 33.

five experiments the drug was given intravenously, most of it having left the circulation at the conclusion of the injections, as Dr. Balls was able to find less than 1 mg. in 25 cc. of blood. Failure to bring about any obvious changes in the respiration and the absence of any tendency to sleep on the part of the addicts prove the ineffectiveness of these large doses in bringing about the normal pharmacologic action of morphine on the central nervous system. Several conclusions are to be considered in this respect: First, the additional amounts have no effect on the central nervous system, the latter having become tolerant to large as well as to small amounts; second, the additional amounts must be either rapidly excreted or removed from the blood by tissues other than those of the central nervous system and destroyed, or chemically bound and made inert, and slowly returned to the blood for excretion. The latter conclusion is that of Terruchi and Kai,[3] who worked with rabbits.

Faust [4] attributed tolerance in dogs addicted to morphine to a mechanism developed in them which rapidly destroyed the morphine, as he was unable to recover any in their feces. Rubsamen [5] agreed with Faust that there was increased destruction but was able to recover sufficient morphine from tolerant rats to kill nontolerant rats. Rubsamen concluded, then, that there must be not only an increased destruction but also an increased tolerance on the part of the central nervous system. Terruchi and Kai [3] recovered quantities of morphine from the muscles and small amounts from the liver and brain of addicted rabbits. In their conclusions, Terruchi and Kai stated: "We venture to conclude that the morphinism is due to the acquired power of the living organism to destroy morphine, and to excrete it besides the augmented power to reserve it in a large amount by the muscles, so that even though a large amount of it should be introduced into the body all at once it can be prevented from immediately attacking the central nervous system."

In consideration of the work just cited and our own experiments, we believe that these large amounts of morphine introduced into the circulation are promptly removed by the muscles, so that only small quantities are available for action on the central nervous system. Having once been removed by the muscles, the morphine must have been destroyed or returned slowly to the circulation in small quantities, as Dr. Balls was able to detect only the slightest amounts in the blood. The regular return of craving for the drug on the part of the addicts

3. Terruchi, Yutaka; and Kai, Sotaro: On the Fate of Morphine Which Has Been Injected into the Animal Body, J. Pharm. & Exper. Therap. **31**:177, 1927.

4. Faust, E. S.: Ueber die Ursachen der Gewöhnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **44**:217, 1900.

5. Rubsamen, W.: Experimentelle Untersuchungen über die Gewöhnung an Morphin, Arch. f. exper. Path. u. Pharmakol. **59**:227, 1908.

within a period of three or four hours would indicate, on the other hand, a rather rapid destruction in the muscles, or a quick elimination. Using the hypothesis of Terruchi and Kai,[5] one can find a plausible explanation for the frequency with which the addict increases the amounts required for his need. With the development of a mechanism in the muscles for the removal of morphine from the circulation, one can conceive of it becoming so effective as to leave an insufficient quantity for action on the central nervous system and the addict consequently increasing his regular dosage.

We believe from indirect evidence and the behavior of addicts in general that the quantity of morphine required to prevent the appearance of withdrawal symptoms to be considerably less than is normally used by them. This evidence is based on the following observations. All of our patients who have taken a cure either in our ward or in other institutions and who have had a relapse always begin the use of the drug again in small quantities, rarely more than from ¼ to ½ grain (0.01 to 0.03 Gm.) at each injection. These amounts are ample to restore them to what they consider their normal feeling and also to give them the so-called "kick." These amounts suffice for various lengths of time, and as soon as the "kick" is no longer obtained the addict begins increasing the amounts taken. Our experience with reducing the doses results in little complaint on the part of the patient regardless of the amounts being used or the speed of reduction until the point is reached where the individual dosages are reduced from ½ grain to lower amounts. It is at this point that the addict becomes exceedingly difficult to handle and presents withdrawal symptoms.

Another phase in this problem of the amounts required to prevent withdrawal symptoms is the existence of two more or less ill defined groups of addicts which they themselves classify as "users" and "hogs." One also encounters two mental states following the use of morphine in which the addicts say that they feel "normal" or that they feel "loaded." The group of so-called "users" are able to get along nicely over a period of years on small daily dosages, but nevertheless require these small dosages to prevent withdrawal symptoms. The other group consists of those who are not content to feel normal but who are constantly desirous of being "loaded," and it is the persons in this group who continually increase the amounts taken and are forced to take a cure, after which they are able to begin all over again with small amounts.

Our experience with addicts and all cures, including "cold turkey,"[6] is that at the end of the week to ten days all acute withdrawal symptoms have disappeared. The addict is now able to satisfy his craving as well as to derive a "kick" with dosages as low as from ⅛ to ¼ grain (8 to 16 mg.).

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6. Abrupt withdrawal without the substitution of any drug.

If ignorant of this small requirement, the addict may take his regular dosage and suffer serious results and even death. One of our patients died suddenly following discharge from the hospital after taking an injection of the same quantity used before the cure was taken. These sudden deaths are not infrequent, according to addicts, although the reliability of their statements must always be questioned.

It would appear, then, on the basis of the conclusions of Terruchi and Kai that within a week or ten days the muscles lose their ability to remove the drug from the circulation, and that small quantities will again suffice to give the addicts their feeling of normality or "kick." Furthermore, the foregoing theory still being used as an explanation, the ability of the muscles to remove the morphine from the circulation is not brought into play until dosages in excess of those required to prevent withdrawal symptoms are used.

This application of the theory of Terruchi and Kai does not, however, offer any explanation as to the cause of the appearance of the withdrawal symptoms nor the presence of the craving for the drug after the acute withdrawal symptoms have disappeared. Marme [7] attributed the cause of the withdrawal symptoms to the presence of pseudomorphine and believed that additional amounts of morphine were required to counteract the presence of the pseudomorphine. This work has been criticized by Donath,[8] Stark,[9] Marquis,[10] Toth [11] and Gioffredi,[12] in a review of the literature on tolerance and withdrawal phenomena by Du Mez.[13] Before accepting any explanations or theories as to what has happened to the morphine, one should know whether these large quantities are rapidly excreted in human addicts, by what channels, and whether morphine is still being excreted while withdrawal symptoms are present. Such experiments are planned and will be carried out as our next step in the study of opium addiction.

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7. Marme, W.: Untersuchungen zur acuten und chronischen Morphin-Vergiftung, Deutsche med. Wchnschr. **9**:197, 1883.

8. Donath, J.: Das Schicksal des Morphins im Organismus, Arch. f. d. ges. Physiol. **38**:528, 1886.

9. Stark, E.: Untersuchungen uber die Gewohnung des thierischen Organismus an Gifte; Inaug. Diss., Erlangen, 1887; cited by Faust, Arch. f. exper. Path. u. Pharmakol. **44**:225, 1900.

10. Marquis, E. P.: Ueber den Verbleib des Morphins im thierischen Organismus, Pharm. Ztschr. f. Russland **35**:549, 1896.

11. Toth, L.: Bemerkungen zur Erklarung der chronischen Morphiumintoxikation, Schmidt's Jahrb., 1891, vol. 229, p. 135.

12. Gioffredi, Carlo: Recherches ulterieures sur l'immunisation pour la morphine, Arch. ital. de biol. **31**:398, 1899.

13. Du Mez, A. G.: Increased Tolerance and Withdrawal Phenomena in Chronic Morphinism, J. A. M. A. **72**:1069 (April 12) 1919.

CONCLUSIONS

The intramuscular injection of morphine sulphate in dosages of three, four and six times the usual amounts given, and the intravenous injection of dosages six, seven and nine times the amounts usually given to the human opium addicts who acted as subjects resulted in insignificant changes in the pulse and respiration rates, electrocardiogram, chemical studies of the blood, and the behavior of the addict.

The intravenous administration of 20 grains and 11 grains to two different addicts following a forty-eight hour withdrawal period also failed to produce any significant physiologic changes or changes in behavior after fifty-six minutes and one hour and sixteen minutes, respectively.

Analyses of the blood for morphine showed the presence of less than 1 mg. per 25 cc. of blood, indicating its rapid removal following the completion of the injection.

THE ARTERIOLES IN CASES OF HYPERTENSION*

JAMES W. KERNOHAN, M.B.

EDWARD W. ANDERSON, M.D.

AND

NORMAN M. KEITH, M.D.

ROCHESTER, MINN.

For the last sixty years many have studied the histologic changes in the smaller arteries in diffuse disease of the vascular system. There has been considerable controversy as to whether any characteristic pathologic lesion is present. Our interest in this subject was renewed when the ophthalmologist was so frequently able to demonstrate narrowing of the retinal arteries and arterioles in cases of malignant hypertension. A year ago Keith, Wagener and Kernohan [1] were able to show in such a case that there were common features in the smaller arteries and arterioles in many organs, including those supplying the voluntary muscle. The latter observation suggested that biopsy material from a superficial muscle in ambulatory cases of hypertension might show early histologic changes in the smaller arteries. Muscle tissue was chosen because it composes about 35 to 40 per cent of the body and thus an assumption that there is a widespread lesion of the arterioles could be readily proved or disproved.

LITERATURE

The pertinent literature of the last sixty years has been reviewed. In 1868, Johnson [2] systematically studied the smaller arteries of most of the tissues in cases of chronic Bright's disease. He demonstrated thickening of the media, or muscular coat, and concluded that there was an arterial hypermyotrophy similar in cause to the hypertrophy of the heart muscle. Gull and Sutton [3] were unable to find such thickening of the media, and in 1872 they concluded, from their studies of similar cases,

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* From the Section on Pathologic Anatomy and the Division of Medicine, the Mayo Clinic.

1. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141 (Feb.) 1928.

2. Johnson, George: On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney: II. On the Influence of the Minute Blood-Vessels upon the Circulation, Tr. Medico-Chir. Soc. London **51**:57, 1868.

3. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called "Chronic Bright's Disease with Contracted Kidney," Tr. Medico-Chir. Soc. London **55**:273, 1872.

that the lesion in the smaller arteries was of a hyaline, fibroid, degenerative type. Five years later, Ewald [4] investigated a large series of these cases, and his observations confirmed the presence of hypertrophy of the media first described by Johnson. He particularly called attention to the increased thickness of the walls of the vessels and the narrowed lumen. It should be pointed out, however, that this early work was done before the present histologic technic was devised; therefore, it is difficult to draw definite conclusions from it.

Using modern histologic technic in a large series of such cases, Jores,[5] in 1904, carried out a thorough and comprehensive study of the small visceral arteries. The specific vascular change which he observed was characterized by degenerative processes in the intima, hyaline and fatty changes, and a hyperplastic thickening of the internal elastic membrane. He noted also that this lesion was more frequently found in the small arteries of the kidney, the spleen and the pancreas, and he specifically stated that when the lesion was widespread in many different organs he was unable to demonstrate it in the skeletal muscle. Jores considered it possible that hypertrophy of the muscular coat sometimes occurs, but that this hypertrophy is not specific or prominent and that it may be due to postmortem contraction. In contrast to these generalizations, it is significant that he mentioned the case of a young man, aged 24, with aortic insufficiency due to rheumatic endocarditis, in whom there was definite thickening of the muscle of the media of the arterioles in many organs, including arterioles of the skeletal muscle. He also noted that in this case the thickness of the wall was considerably increased in relation to the diameter of the lumen. Omission of a reading of the blood pressure in this case is regrettable, even though the case occurred before clinical determinations of the blood pressure were made as a routine. Jores' statement has been generally accepted, that when there is a diffuse lesion of the arterioles, it is chiefly of a degenerative nature and is limited to the intima. In 1910, Fischer and Schlayer [6] noted that peripheral arteries, which on palpation seemed thickened, when examined histologically frequently did not show any intimal change. They stressed the absence of intimal change and suggested that although hypertrophy of the media is difficult to demonstrate, it is sometimes present, and may be of

4. Ewald, C. A.: Ueber die Veränderungen kleiner Gefässe bei Morbus brightii und die darauf bezüglichen Theorien, Virchows Arch. f. path. Anat. **71**:453, 1877.

5. Jores, L.: Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, Virchows Arch. f. path. Anat. **178**:367, 1904.

6. Fischer, Heinrich; and Schlayer: Arteriosklerose und Fuhlbarkeit der Arterienwand, Deutsches, Arch. f. klin. Med. **98**:164, 1910.

great significance in early arterial disturbances. Fahr [7] and Herxheimer [8] noted that the lesion described by Jores was chiefly limited to the renal arterioles and was not widespread in arterioles of other organs. Fahr,[9] in 1916, described a series of cases in which changes in the renal arterioles were marked, with thickening and even necrosis of the vascular walls; these secondarily caused distinct changes in the renal parenchyma. He termed the condition malignant renal sclerosis, since renal insufficiency was present and the prognosis was unfavorable. Fahr, in 1919 and 1920, emphasized the special features of the lesion and intimated the possibility of a toxic etiologic factor. He also pointed out that the lesion usually occurred in persons aged less than 50, whereas senile arteriosclerotic changes were most common in older persons. Both Herxheimer [10] and Stern [11] reported cases of malignant sclerosis of the renal vessels, with changes in the renal arterioles, as described by Fahr. However, they did not wholly accept his theory as to a possible toxic causative agent. In two long, comprehensive articles, in 1922 and 1925, Fahr [12] discussed his observations in a series that included cases of benign and cases of malignant sclerosis. He again stated that the arterioles of organs other than the kidney and particularly those of the skeletal muscle, the skin and the intestine are relatively free from arteriosclerotic degenerative changes. He did note that in the arterioles of the skin, the intestine and especially the skeletal muscle, the media is well developed, contrary to the condition in the renal arterioles, in which the media is reduced. Fahr concluded that malignant renal sclerosis develops as a result of parasitic or chemical poisons, causing a "necrotizing arteriolitis," whereas benign sclerosis results from wear and tear, giving rise to a degenerative type of sclerosis. He believed that the constant hypertension in both groups is of renal origin.

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7. Fahr, T.: Zur pathologisch-anatomischen Unterscheiding der Schrumpfnieren nebst Bemerkungen zur Arteriosklerose der kleinen Organarterien, Frankfurt. Ztschr. f. Path. **9**:15, 1912.

8. Herxheimer, Gotthold: Niere und Hypertonie, Verhandl. d. deutsch. path. Gesellsch. **15**:211, 1912.

9. Fahr, T.: Ueber maligne Nierensklerose (Kombinationsform), Centralbl. f. allg. Path. u. path. Anat. **27**:481, 1916.

10. Herxheimer, Gotthold: Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **251**:709, 1924.

11. Stern, Max: Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem macroskopischen Bilde der "Grossen bunten Niere," Virchows Arch. f. path. Anat. **251**:718, 1924.

12. Fahr, T.: Ueber die Beziehungen von Arteriolensklerose, Hypertonie und Herzhypertrophie, Virchows Arch. f. path. Anat. **239**:41, 1922; Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6, pt. 1, p. 121.

Evans [13] investigated the lesions in the arteries and arterioles of many organs in a large series of cases. The tissues examined were removed during operation or at necropsy. The ages of the patients varied from 8 to 86 years. In cases with hypertension and cardiac hypertrophy, he invariably demonstrated the characteristic changes of diffuse hyperplastic sclerosis in many arterioles. The criteria on which he made a diagnosis of this lesion were: (1) proliferation and then degeneration of the intima; (2) thickening of the media due to hypertrophy of the muscle, with lack of evidence of any degenerative changes in this layer. The organs the arterioles of which usually showed this change were the kidney and the spleen. The change occasionally was present elsewhere in lesser degree, but practically never in heart or skeletal muscle. Evans believed that his observations indicate that diffuse hyperplastic sclerosis of the arterioles is similar in children and in adults, that it can be distinguished from senile arteriosclerosis, that it is probably inflammatory and that the diffuse arteriolar and renal lesions are the simultaneous results of a single pathogenic agent.

Fishberg [14] made a similar study in a large series of cases of essential hypertension. Like Jores, Fahr and Evans, he found that atrophy of the media was the rule, and that rarely were there any noticeable changes in the arterioles of voluntary muscle. Similar negative observations were made in the arterioles of voluntary muscle by Branch and Linder [15] in six cases of chronic glomerulonephritis occurring in young persons. Fishberg [16] did find hypertrophy of the media in the renal arterioles, but not elsewhere in certain cases of chronic glomerulonephritis. Brogsitter [17] examined the mesenteric vessels in thirty-three cases of hypertension. He found thickening of the media in some cases, with the muscle layer rich in nuclei, changes which he interpreted as being the result of maximal contraction. He did not find any relationship between the height and the duration of the hypertension and the changes in the mesenteric arteries. Michel,[18] in 1884, in an ophthalmoscopic

13. Evans, Geoffrey: A Contribution to the Study of Arterio-Sclerosis with Special Reference to Its Relation to Chronic Renal Disease, Quart. J. Med. **14**: 215, 1920-1921; Arteriosclerosis in Children, ibid. **16**:33, 1922-1923.

14. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650 (May) 1925.

15. Branch, Arnold; and Linder, G. C.: The Association of Generalized Arteriolar Sclerosis with High Blood Pressure and Cardiac Hypertrophy in Chronic Nephritis, J. Clin. Investigation **3**:299, 1926.

16. Fishberg, A. M.: Arteriolar Lesions of Glomerulonephritis, Arch. Int. Med. **40**:80 (July) 1927.

17. Brogsitter, A. M.: Zur Anatomie der Splanchnikusgefässe beim Hochdruck, München. med. Wchnschr. **2**:1049, 1924.

18. Michel, Julius: Lehrbuch der Augenheilkunde, Wiesbaden, J. F. Bergmann, 1884.

study of the retina in patients with general arteriosclerosis and nephritis noted the presence of sclerosis of the retinal arteries. Karl,[19] in 1887, described this sclerosis in the retinal and choroidal arteries as the primary pathologic basis of "albuminuric retinitis." He found, histologically, arteritis of the retinal and choroidal arteries, which terminated in hyaline thickening and degeneration of all the coats. Gunn,[20] in 1898, noted in cases of general arteriosclerosis the uniform constriction of the retinal arteries and the ischemic features of the frequently associated retinitis. Coats [21] showed that the histologic basis of this apparent constriction of the retinal arteries was an increase of the fibrous tissue in the media and the adventitia. Only rarely was there proliferation of the endothelium. Leber,[22] in 1915, observed, in cases of retinitis of nephritis, hypertrophy of the muscular coat of the central retinal and posterior ciliary arteries. He considered that the ophthalmoscopic evidence of retinal arteriosclerosis, in the absence of retinitis, was due to endarteritis with subendothelial intimal proliferation. He also suggested that in some cases the appearance of the arteries might be due to tonic contraction without demonstrable histologic changes. Volhard,[23] in 1921, emphasized the angiospastic features of "albuminuric retinitis" in chronic glomerulonephritis and in malignant renal sclerosis. Cohen [24] found, histologically, marked thickening of the vessels in the choroid and the retina of patients with diffuse vascular disease. Keith, Wagener and Kernohan,[1] in their study of the syndrome of malignant hypertension, emphasized the presence of a lesion in the arterioles throughout the body. This lesion was observed during life in the retina and histologically in both the retina and the choroid. The characteristics of this lesion were the same in the different tissues examined, which included all the important organs of the body. The three anatomic divisions of the walls of the arterioles were thickened or hypertrophied, especially the intima and the media, with an almost total absence of signs of degeneration.

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20. Gunn, Marcus: On Ophthalmoscopic Evidence of General Arterial Disease, Tr. Ophth. Soc. U. Kingdom **18**:356, 1898.

21. Coats, George: Intraocular Vascular Disease, Ophthalmoscope **4**:605, 1906.

22. Leber, T.: Die Krankheiten und Anomalien des Blutgefäss Systeme der Netzhaut, in Graefe-Saemisch: Handbuch der gesamten Augenheilkunde, Leipzig, Engelmann, 1915, vol. 2, p. 101.

23. Volhard, F.: Ueber die Retinitis albuminurica, Verhandl. d. Kong. f. inn. Med. **33**:422, 1921.

24. Cohen, Martin: Significance of Pathologic Changes in Fundus in General Arterial and Kidney Diseases, J. A. M. A. **78**:1694 (June 3) 1922.

CLINICAL OBSERVATIONS

Hypertension has been classified as benign and malignant with the retinal picture as one of the most significant diagnostic points in the latter. However, there is a group of cases of hypertension in which it is difficult to make such a differentiation. In this study, we have grouped these intermediate cases as those of severe benign or early malignant hypertension.[25] Fifty-three cases were studied and biopsy was done; eleven cases were diagnosed as benign, eighteen as severe benign or early malignant, and twenty-three as malignant hypertension. The remaining case, one of chronic glomerulonephritis, was studied for comparison with the cases of diffuse vascular hypertensive disease. Complete vascular and renal studies were made in the hospital in most of the cases, and at the same time the biopsy was done. The clinical data will be found in detail in table 1.

Benign Hypertension.—In this group, the longest duration of known hypertension was fifteen years; in other cases, the patients did not know that they had hypertension until it was discovered on examination in the clinic. The average duration was five years and eight months. The ages varied from 30 to 65 years, with the average at 47 years. The following are abstracts of illustrative cases.

CASE 10.—A physician, aged 30, discovered in himself eight years before admission a blood pressure of 140 systolic and 100 diastolic and symptoms of palpitation and heart consciousness. He was in good physical condition when he came to the clinic in October, 1928. The blood pressure varied from 155 to 180 systolic, and from 120 to 125 diastolic. There was mild cardiac hypertrophy, peripheral arterial sclerosis grades 1 to 2, no retinitis and slight retinal sclerosis. The blood urea was normal. The urine was clear, except for a trace of albumin. The electrocardiographic report did not reveal anything significant.

CASE 6.—A man, aged 51, was first seen in April, 1927; at this time his chief complaint was nervousness. The systolic blood pressure was 200 and the diastolic 130 on first examination. Later it was 120 systolic and 85 diastolic. A diagnosis of benign hypertension, migraine and vasomotor instability was made. He returned for reexamination in August, 1927; at this time the blood pressure varied from 190 to 140 systolic and from 125 to 90 diastolic. On his last visit, in May, 1928, he complained of dizzy spells; his blood pressure was 210 systolic and 115 diastolic. On later examination, it was 110 systolic and 90 diastolic.

The general examination was essentially negative, except for nervous instability. The heart was slightly enlarged and there was mild sclerosis of the peripheral and retinal vessels. The blood count and urinalysis did not reveal anything abnormal. The renal function was satisfactory. The electrocardiogram was negative. Examination of the peripheral capillaries at the nailfold disclosed mild contraction with slightly increased mechanical flow. A recent communication from the patient stated that he was in good condition and was working daily.

25. Adams and Brown (Considerations on the Treatment of Essential Hypertension, Ann. Clin. Med. **5**:1036, 1927) studied a similar group of cases. Many of the present series are distinguished from theirs in that retinal, renal and cardiac functions often were well maintained at the time of examination.

CASE 3.—A woman, aged 38, came to the clinic on May 2, 1928, complaining of high blood pressure and of headaches of one and a half years' duration. She had been married ten years and had two children, 8 and 6 years of age. The blood pressure had been normal during pregnancy and albuminuria had not occurred. In the course of the third pregnancy, in December, 1926, she had become unconscious and had been blind for two or three weeks. The blood pressure then had been found to be 230 systolic and albuminuria had been present. She had been sent to a hospital and the pregnancy had been terminated. Since then she had had constant headache, some decrease in vision and slight dyspnea.

General examination at the clinic revealed a well developed and well nourished woman with a blood pressure varying from 220 to 140 systolic and from 130 to 95 diastolic. The heart was normal in size and there was only slight peripheral arterial sclerosis. The arteries of the retina were markedly contracted, with sclerosis, grades 1 to 2. There were questionable signs of healed retinitis. Examination of the blood and the urine did not reveal anything abnormal and renal function was satisfactory. The electrocardiogram was negative. The capillaries at the nailfold were moderately contracted and flow was swift.

Severe Benign or Early Malignant Hypertension (Intermediate Group).—In this group, the duration of known hypertension varied from fifteen years to two months, with an average of four years. The variation in age was from 21 to 59 years and the average was 47 years. The following are abstracts of illustrative cases.

CASE 15.—A woman, aged 23, registered at the clinic in May, 1928, complaining of headaches that had been recurring since November, 1927. At the time of the onset, her college physician had noted tachycardia with a rate of 110, which was reduced by digitalis to 80. Hypertension also was found and was treated with salts and Turkish baths.

The general examination was negative except for slight cardiac hypertrophy. The blood pressure varied from 205 to 140 systolic and from 160 to 100 diastolic. There was retinal sclerosis, grade 1, but peripheral sclerosis or retinitis was not present. The blood and the urine did not reveal anything abnormal and the renal function was satisfactory. The electrocardiogram was negative. There was mild contraction with moderate tortuosity of the capillaries at the nailfold, and there was fast mechanical flow. A recent communication from the patient stated that she was working regularly every day.

CASE 28.—A man, aged 22, was last seen at the clinic in November, 1927. In January, 1927, he had come to the clinic complaining of headaches that had been recurring during the past two years. He had passed an examination for life insurance in 1924. The blood pressure in September, 1926, had been 220 systolic. The blood pressure in January, 1927, had been 230 systolic and 150 diastolic. A diagnosis was made of essential hypertension (premalignant) and generalized arteriosclerosis. In November, 1927, the blood pressure was 245 systolic and 140 diastolic. Later it was 155 systolic and 105 diastolic.

There was mild cardiac hypertrophy with peripheral sclerosis, grade 2. There was no retinitis; the retinal arteries were mildly sclerosed. The blood count was normal, and the renal function was satisfactory. Electrocardiographic observations did not indicate any abnormality. The capillaries at the nailfold were mildly contracted and tortuous, and flow was swift.

TABLE 1.—*Results of Vascular and Renal Studies and Biopsy Made on Persons with Hypertension*

Case	Hypertension	Sex	Age	Blood Pressure: Maximum: Systolic	Blood Pressure: Maximum: Diastolic	Blood Pressure: Minimum: Systolic	Blood Pressure: Minimum: Diastolic	Cardiac Hypertrophy*	Fundus: Peripheral Sclerosis*	Fundus: Retinitis*	Fundus: Sclerosis*	Blood: Ratio of Wall to Lumen of Arteriole in Muscle	Blood: Hemoglobin, per Cent (Dare)	Blood: Erythrocytes, Millions	Blood: Urea, Mg. per 100 Cc.	Urine: Specific Gravity: Maximum	Urine: Specific Gravity: Minimum	Urine: Albumin*	Urine: Phenolsulphonphthalein, per Cent	Electrocardiogram	Capillaries: Tortuosity*	Capillaries: Flow (M Denotes Mechanical)*	Capillaries: Contraction*
1	Benign	M	44	235	145	180	90	1	2+	3	3	1:1.30	60	3.22	48	1.016	1.004	2	35	Inverted T wave leads I and II.....	2	2	1
2	Benign	F	55	240	120	140	80	§	1	1	2	1:1.20	70	4.51	26	1.030	1.001	¶	60	Diphasic T wave lead I.....	0	3M	1+
3	Benign	F	38	220	130	140	95	0	§	?	1+	1:1.40	68	4.08	18	1.010	.....	0	75	Essentially negative	0	3	2
4	Benign	M	50	210	140	150	95	2	2	0	1	1:1.4**	76	4.60	34	1.026	.....	0	85	Essentially negative	0	1	2
5	Benign	M	42	210	140	130	75	1	3	3	3	1:1.2	76	4.31	24	1.025	1.002	2	75	Inverted T wave leads I and II.....	0	0	§
6	Benign	M	51	210	115	110	90	1	1+	0	1	1:1.8	79	4.88	25	1.025	1.001	0	70	Essentially negative	0	1M	1
7	Benign	M	57	200	120	130	70	1	2+	0	§	1:1.5	79	4.94	30	1.027	1.002	0	50	Diphasic T wave leads II and III.....	2	2M	1
8	Benign	M	65	180	100	140	90	1+	1+	0	1+	1:1.26	77	4.05	40	1.020	1.002	0	45	Essentially negative	1+	2	0
9	Benign	M	41	180	130	140	90	1	2+	0	1+	1:1.3	77	4.65	32	1.027	1.003	2	75	Essentially negative	0	2	1
10	Benign	M	30	180	125	155	120	1	1+	0	§	1:1.7	71	4.66	26	1.028	.....	1	85	Inverted T wave lead III.....	.	.	.
11	Benign	F	41	200	125	125	70	§	2	2	3	1:1.5	71	3.98	35	1.010	1.006	3	35	Inverted T wave lead I.....	1	0	0
12	Severe benign.	M	54	200	140	130	80	1	1+	1+	2	1:1.1	73	....	33	1.026	1.003	0	50	Diphasic T wave lead I.....	.	.	.
13	Severe benign.	M	22	200	140	135	90	§	§	0	1	1:1.6	80	4.45	28	1.025	1.002	2	40	Essentially negative	.	.	.
14	Severe benign.	M	59	185	115	130	70	2	2+	0	3	1:0.8	78	4.53	38	1.032	.....	0	40	Inverted T wave leads II and III.....	1	2	1
15	Severe benign.	F	23	205	160	140	100	§	0	0	1	1:1.05	75	4.72	15	1.028	1.001	0	75	Essentially negative	2	2M	1
16	Severe benign.	F	39	250	140	190	105	1	1	1	2	1:1.2	71	4.30	20	1.030	.....	2	55	Inverted T wave leads I and II.....	.	.	.
																		..		Diphasic T wave lead III.....	.	.	.
17	Severe benign.	M	39	190	140	125	100	1	1+	2	1	1:1.0	76	4.90	35	1.015	1.003	2	40	Inverted T wave leads I and II.....	.	.	.
18	Severe benign.	M	21	190	140	150	100	2	2	0	1	1:1.06	78	4.99	28	1.023	1.002	2	40	Inverted T wave lead I.....	1	2M	2
																		..		Diphasic T wave lead II.....			
19	Severe benign.	F	38	240	160	150	110	1	§	0	1+	1:1.4	78	4.76	30	1.030	1.001	2	25	Essentially negative	1	2	1
20	Severe benign.	M	42	230	155	175	130	1	2+	3	3	1:1.2	74	4.04	54	1.016	1.003	2	30	Inverted T wave leads I and II.....	1	3M	2
21	Severe benign.	M	57	280	140	170	90	3	3	3	3	1:1.7	70	4.71	45	1.026	.....	3	40	Inverted T wave leads I and II.....	.	.	.
																		..		Slurred T wave lead III..	1+	2	1+
22	Severe benign.	M	54	270	140	160	100	1+	2+	1	2+	1:1.3	78	4.20	27	1.030	1.001	0	60	Essentially negative	.	.	.
23	Severe benign.	F	23	225	160	175	110	1	2	1	1+	1:1.2	75	4.10	37	1.021	1.003	¶	60	Inverted T wave leads I and II.....	1	2	.
24	Severe benign.	M	48	200	130	160	80	2	2+	1	1+	1:1.2	75	4.11	38	1.020	1.002	2	25	Auricular premature contraction.....	0	2	1
25	Severe benign.	M	51	225	140	175	110	1	2	1	2	1:1.1	68	4.46	30	1.010	.....	.	65	Essentially negative	1	3M	1

26	Severe benign.	M	37	255	155	170	110	1	1	0	1+	1:1.07	75	4.66	36	1.022	1.003	2	55	Inverted T wave lead I	.	.	.
																		.	..	Diphasic T wave lead II	0	3M	2
27	Severe benign.	F	56	260	160	165	100	1	1+	1	2	1:1.4	73	4.22	38	1.022	1.002	3	50	Inverted T wave leads I, II and III	0	2	2
28	Severe benign.	M	22	245	140	155	105	1	2	0	1	1:1.05	80	4.79	22	1.010	.....	0	85	Essentially negative	1	2	1
29	Severe benign.	M	48	240	160	175	110	1	2	0	1	1:1.20	77	4.74	23	1.018	1.003	3	50	Inverted T wave leads I and II	0	2M	1
30	Malignant	M	52	240	150	210	110	2	3	3	3	1:1.09	60	3.64	133	1.010	1.007	3	2	Inverted T wave leads I and III	2	2	1
31	Malignant	M	45	235	160	195	120	2	3	1	3	1:1.30	77	4.44	37	1.021	.....	2	35	Inverted T wave leads I and II	1	3	3
32	Malignant	M	34	245	145	175	120	2	1	2	3	1:1.20	72	4.88	34	1.024	1.001	2	35	Inverted T wave leads I and II	0	2	1
33	Malignant	M	26	220	170	170	130	1+	1+	3	2	1:1.2	80	4.57	41	1.025	1.002	3	45	Inverted T wave leads I and II	0	3	2
34	Malignant	M	50	320	175	170	80	1+	2	1	2	1:1.1	77	5.02	30	1.024	1.003	¶	35	Diphasic T wave leads I and II	.	.	.
																		.	..	Inverted T wave lead III	2	3	3
35	Malignant	M	55	270	170	180	110	1	2+	2	2	1:1.2	60	3.90	38	1.014	1.002	2	45	Inverted T wave lead I	1	3M	0
36	Malignant	M	55	220	140	155	105	1	2+	2+	3	1:1.2	75	4.80	64	1.020	1.003	2	25	Essentially negative	1	2M	0
37	Malignant	M	54	230	140	160	100	1	2+	2	2+	1:1.3	80	4.26	38	1.023	.....	2	35	Essentially negative	1	2	1
38†	Malignant	F	8	210	145	150	120	1	1	1	2	1:1.2	71	4.50	36	1.020	1.004	2	70	Not taken	2	2	.
39	Malignant	M	51	235	165	200	110	2	2+	2	2+	1:1.1	72	4.44	34	1.015	.....	2	40	Inverted T wave lead I	0	3M	2
40‡	Malignant	M	23	200	145	180	140	1	1+	2	1	1:1.2	80	4.96	22	1.020	.....	0	50	Inverted T wave leads I and II	.	.	.
																		.	..	Coronary T wave leads I and II	.	.	.
41	Malignant	M	42	230	145	145	110	1+	2	2	2	1:1.05	82	4.84	34	1.025	1.002	2	60	Diphasic T wave lead I	.	.	.
																		.	..	Inverted T wave leads II and III	0	0	1
42	Malignant	M	55	255	150	200	110	2	2	2	3	1:1.3	75	4.44	41	1.019	1.002	1	30	Inverted T wave leads I, II and III	.	.	.
43	Malignant	M	48	200	150	190	100	2	2+	1	2+	1:1.0	85	4.16	35	1.019	1.003	2	30	Essentially negative	1	2M	2
44	Malignant	M	38	200	160	190	125	2+	2	2	3	1:1.2	78	4.53	53	1.015	1.003	2	25	Inverted T wave leads I and II	0	3M	0
45	Malignant	F	34	165	110	120	80	§	1	2	?	1:1.2	75	4.38	24	1.035	1.002	0	70	Essentially negative	1	3M	0
46	Malignant	M	48	220	165	160	110	1	3	2	3	1:1.0	73	4.27	60	1.020	1.010	3	30	Inverted T wave leads I and II	2	2	2
47	Malignant	M	58	230	140	160	80	2	2	2	2	1:1.4	44	3.06	97	1.013	1.002	3	10	Inverted T wave leads I, II and III	0	3M	2
48	Malignant	M	49	220	130	160	110	1	3	?	3+	1:1.1	72	4.39	30	1.024	1.002	0	40	Diphasic T wave lead I	0	3M	2
49	Malignant	M	49	260	180	155	110	1	3	3	3	1:1.0	68	3.98	49	1.017	1.002	¶	45	Inverted T wave lead III	1	3M	0
50	Malignant	M	54	255	160	140	60	1	2+	2	2	1:1.0	76	4.41	40	1.010	.....	2	35	Inverted T wave leads I and II	0	3	1
51	Malignant	M	51	260	180	210	130	1+	3	2	3	1:1.0	68	4.09	72	1.008	.....	2	10	Inverted T wave lead I	.	.	.
																		.	..	Diphasic T wave lead II	1	2M	2
52	Malignant	M	49	250	160	200	135	2	2+	2	3	1:1.2	92	4.62	36	1.019	.....	2	30	Ventricular premature contraction	0	2	1
53	Chronic glomerulonephritis	F	46	170	100	115	70	0	§	0	§	1:1.8	67	4.30	56	1.020	.....	4	55	Inverted T wave lead III	0	2	1

* Graded on a basis of 1 to 4.
** Same ratio at second biopsy nine months later.
† Case reported by Amberg, Samuel: Hypertension in the Young, Am. J. Dis. Child. **37:** 335 (Feb.) 1929.
‡ Only case in which the Wassermann reaction of the blood serum was positive.
§ Slight.
¶ Trace.

Malignant Hypertension.—This group showed the characteristics described in a previous paper by Keith, Wagener and Kernohan.[1] The duration of known hypertension in some cases was seven years; in others, the patients were not aware that they had hypertension until it was discovered at the clinic. The average duration of the disorder was two years and eight months. The ages varied from 8 to 55 years, with an average of 45 years. The following are abstracts of illustrative cases.

CASE 33.—A man, aged 26, entered the clinic on March 6, 1928, complaining of high blood pressure, which had been discovered in an examination for insurance one year before. At that time, the systolic pressure was 200. Slight dyspnea had been present for six months and there had been nocturia and easy fatigue for three or four months. There had been blurring of vision for three weeks. During the year he had lost 43 pounds (19.5 Kg.).

The patient appeared ill at the time of the general examination. The heart was moderately hypertrophied and there was peripheral sclerosis, grade 1 +. The patient's blood pressure was 220 systolic and 170 diastolic, on one occasion, and later it was 170 systolic and 130 diastolic. There was retinitis, grade 3, with edema of the disks of 2 diopters, hemorrhages, exudate and incomplete macular stars in both eyes. The blood count was normal. There was marked albuminuria with hematuria. In the phenolsulphonphthalein test of renal function there was 45 per cent return of dye in two hours. The blood urea was 41 mg., and electrocardiographic tracings gave evidence of myocardial degeneration as indicated by inverted T waves in leads I and II. There was moderate contraction of the capillaries at the nailfold, with swift flow. The patient died at home during the first week of July, 1928, four months after leaving the clinic.

CASE 45.—A woman, aged 34, registered at the clinic in January, 1928. She complained of attacks of unconsciousness recurring over a period of five years. They were becoming more frequent and had been associated during the previous summer with blurring of vision. She had had an occasional headache. Menopause had occurred at the age of 29.

The patient was well nourished and well developed with a slightly enlarged heart and slight peripheral sclerosis. There was retinitis, grade 2, without retinal sclerosis. Renal function was normal, and the electrocardiogram appeared to be that of a normal condition. Blood pressure, on admission, was 165 systolic and 110 diastolic. Later, it was 120 systolic and 80 diastolic. Neurologic examination did not reveal any abnormality. The cerebrospinal fluid was under increased pressure. More visual disturbance developed subsequently.

CASE 48.—A physician, aged 49, came to the clinic on May 1, 1927. While watching operations at the clinic, he noted tingling in the left arm and leg, with numbness and weakness. He had had scarlet fever with nephritis at the age of 9, and at the age of 29 he had had diphtheria complicated by nephritis and edema of the ankles. At the age of 44, his blood pressure, on examination for life insurance, was 180 systolic, but later it was 145 systolic, and he received a policy for $25,000 without an increase in rates.

The patient's blood pressure at the time of examination was 210 systolic. On May 9, 1927, there were bilateral choked disks of 4 diopters in the right eye and of 2 diopters in the left, with hemorrhage and exudate. The arteries were markedly constricted. The diagnosis of retinitis of malignant hypertension was made. The blood urea was 44 mg. in each hundred cubic centimeters. There was an inverted T wave in lead I of the electrocardiogram. With rest, the blood

pressure was reduced to 170 systolic and 100 diastolic. The cerebrospinal fluid was under a pressure of 36 cm. of water. The edema of the disks cleared and on May 12 there was a choked disk in the right eye of 2 + diopters, and in the left eye of 1 + diopter.

The patient returned on Feb. 20, 1928, for reexamination; the blood pressure was then 220 systolic and 130 diastolic. In the electrocardiogram there was a diphasic T wave in lead I. The optic disks were without edema and the arteries were contracted irregularly. On May 17, the blood pressure was 210 systolic and 135 diastolic. There was an inverted T wave in leads I and II in the electrocardiogram and there was sclerosis, grade 3 +, in the retinal arteries. The optic disks were flat and pale. The patient died on May 24, 1928, following a cerebral hemorrhage.

TABLE 2.—*Clinical Résumé and Comparison of Three Groups of Cases of Hypertension*

Points of Comparison	Benign	Severe Benign or Early Malignant	Malignant
Number of cases	11	18	23
Blood pressure, mm.			
Maximal systolic	240	280	320
Maximal diastolic	145	160	180
Minimal systolic	180	185	165
Minimal diastolic	100	115	110
Systolic more than 250, per cent	...	28	35
Diastolic more than 140, per cent	27	89	95
Cardiac hypertrophy, per cent			
Grade 1	73	67	40
Grade 2	18	28	52
Peripheral sclerosis, per cent			
Grade 2	55	39	30
Grade 3	27	28	57
Retinal sclerosis, per cent			
Grade 1	36	33	4
Grade 2	36	45	30
Grade 3	27	22	62
Albuminuria, per cent			
Absent	45	22	13
Grade 2	27	56	57
Renal insufficiency, per cent			
Absent	73	67	17
Grade 1	27	28	57
Grade 2	...	5	22
Grade 3	...	...	4
No anemia, per cent	91	100	83

Comparison of the Three Groups.—A comparison of the clinical data in the three types of hypertensive vascular disease is made in table 2. If 250 mm. is taken as a level for systolic pressure and 140 mm. as a level for diastolic pressure, it will be seen that in none of the cases of benign hypertension was the systolic pressure more than 250 mm., whereas in each of the other two groups the readings in practically a third of the cases were in excess of this figure. Similar results were obtained in readings of diastolic pressure. Twenty-seven per cent of the cases of benign, 89 per cent of the cases of early malignant and 95 per cent of the cases of malignant hyptertension had a diastolic pressure of 140 mm. or more. On measuring the size of the heart, enlargement, grade 1, was the rule in the cases of the benign group, whereas enlarge-

ment, grade 2, was slightly more common in the cases of the intermediate groups and was present in more than half of the cases of the malignant group.

Peripheral arterial sclerosis, grade 2, was present in 55 per cent of the cases of benign hypertension and in 30 per cent of the cases of malignant hypertension. Grade 3 was found in 27 per cent of the cases of benign hypertension, in 28 per cent of the cases of the intermediate group, and in 57 per cent of the cases of the malignant group. When definite peripheral sclerosis is present in malignant hypertension, the vessel often feels rubbery.

On examination of the retinal vessels, sclerosis, grade 1 or 2, was present in 72 per cent of the cases of benign hypertension and in 78 per cent of the cases of the intermediate group. Sclerosis, grade 3, was present in about 25 per cent of the cases of the benign and intermediate groups and in 62 per cent of the cases of the malignant group. Albuminuria was absent in about half of the cases of benign hypertension, and was graded 2 in about a fourth of them. In the other two groups, it was graded 2 in over half of the cases.

If one considers that a return of 50 per cent or more of phenolsulphonphthalein in two hours, and that 40 mg. of blood urea or less to each hundred cubic centimeters indicate satisfactory renal function, it can be seen that the benign and intermediate groups have satisfactory renal function in the greater percentage, with mild renal insufficiency in a fourth of the cases and moderate renal insufficiency in only 5 per cent of the intermediate group. The malignant group, however, shows mild renal insufficiency in more than half of the cases, moderate insufficiency in 22 per cent and marked insufficiency in 4 per cent.

If one considers 70 per cent hemoglobin (Dare) or more and 4,000,000 or more erythrocytes in each cubic millimeter as within normal limits, it can be seen that anemia is not significant in any group.

In the study of the capillaries at the nailfold, ten cases of benign, thirteen of intermediate and twenty-one of malignant hypertension were reviewed.[26] Straight, mildly contracted vessels and fast mechanical flow were the rule in the cases of benign hypertension. Slight tortuosity, with mild contraction and fast flow, was shown in a greater percentage of cases in the intermediate group, and mechanical flow in about half of the cases. In the malignant group, the flow was fast, with mechanical movement, in half of the cases. The latter observation agrees with our previous observations in the last named group.

Inquiry at the time of writing brought out the fact that, of the eleven patients with benign hypertension, seven were well and four were dead. One death was due to influenza and pneumonia (case 11, table 1). The

26. The nailfold capillaries were examined by G. E. Brown, according to the Lombard technic.

other three deaths had occurred in cases 1, 5 and 8 (table 1). In cases 1 and 8, myocardial degeneration was a prominent feature. In case 5, general and cerebrospinal arteriosclerosis were marked. In the eighteen cases of the intermediate group (table 1), nine of the patients were well, one had suffered an apoplectic stroke and one had lately returned for reexamination, and the picture of the fundus was that of malignant hypertension. Two patients had died. The serious prognosis in the malignant group is again evident.[1] Only two of the twenty-three patients observed were reported as well, two were failing and fourteen had died. Of these fourteen, eleven had died from two to six months after dismissal (average four months).

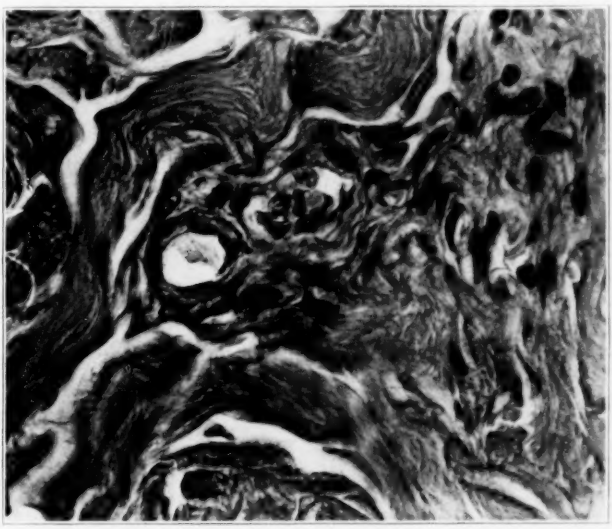

Fig. 1.—A normal arteriole obtained from pectoralis major muscle at necropsy. The comparatively thin wall and absence of signs of hypertrophy of media may be noted. Van Gieson stain; × 600.

HISTOLOGIC STUDIES

Biopsy.—After the injection of a local anesthetic, a small portion of the pectoralis major muscle was removed. This procedure was carried out in the fifty-three cases of the present series. Material for controls was obtained from two sources: from tissue subjacent to breasts amputated for tumors of various types in patients in whom the blood pressure was normal and at necropsy from bodies of patients whose blood pressure had not been elevated and whose hearts had not been enlarged (fig. 1). In one case, a second biopsy was made nine months later and

in two cases in which biopsy was made, necropsy was performed later, and detailed studies were carried out on the arterioles in various organs. All specimens of tissue were embedded in paraffin, were cut at a thickness of 8 microns and were stained with hematoxylin and eosin, with van Gieson's and with Weigert's elastic tissue stains.

The vessels examined were the arterioles. The arteries and capillaries were not included in this study because little histologic change was seen in the capillaries of any patient with high blood pressure, and because it was difficult to obtain regularly larger arteries. We have been unable to find in the literature on anatomy actual measurements of the outside diameter of small vessels, which would permit an accurate measurable distinction between a small artery and an arteriole. Landis,[27] in his micro-injection studies of the blood pressure gradient in the mesentery of the frog, considered an arteriole to be from 40 to 50 microns in diameter. Many pathologists consider the afferent glomerular vessel an arteriole. We have measured a few of these vessels in the normal kidney of man and have found the outside diameter varying from 30 to 50 microns. Landis[28] also directly determined the fall in the blood pressure gradient in arteries, capillaries and veins in the mammalian mesentery. In some later unpublished similar experiments[29] in the rat and guinea-pig, he incidentally measured the diameter of certain of the vessels observed. He classified the vessels as "smallest arteries" and "arterioles" by their relation to the capillary network. The former contained a considerable number of muscle fibers and the diameter measured from 40 to 100 microns, whereas the arterioles, which arise from the smallest arteries and merge into the capillaries, contained fewer muscle fibers and were thinner, measuring from 15 to 35 microns. The diameter of the vessels measured in the present study varied from 25 to 100 microns, so that, from Landis' data, they fall into both his groups of smallest arteries and arterioles.

There were definite changes in the arterioles in many cases and also, to a slight extent, in the surrounding muscle tissue. There was a slight increase in the connective tissue around some of the arterioles and occasionally small collections of lymphocytes, which possibly were the result of the occlusion of some small arterioles. The most pronounced and most constant change observed in the vessels was in the media, which was definitely hypertrophied, and there was an increase in the nuclear elements of this tissue. There was no fibrosis or increase in connective tissue; the entire change was due to proliferation of muscle. Medial

27. Landis, E. M.: The Capillary Pressure in Frog Mesentery as Determined by Micro-Injection Methods, Am. J. Physiol. **75**:548, 1925-1926.

28. Landis, E. M.: Micro-Injection Studies of Capillary Pressure in Mammalian Mesentery, Am. J. Physiol. **85**:387, 1928.

29. Landis, E. M.: Personal communication.

to the muscular elements, the Weigert elastic tissue stain showed that there was also hypertrophy of the internal elastic lamina. In some cases, this was slightly split up, but as a general rule the splitting was not pronounced. In the intima, the change was widely varied, but the most common modification was proliferation of the lining endothelial cells. This sometimes was accompanied by proliferation of the subendothelial tissue, and when both changes were present the vessel was almost occluded. Complete occlusion of a vessel was rare, but partial occlusion was the rule. It does not seem logical to assume that any vasomotor spasm could bring about proliferation of the lining endothelial cells,

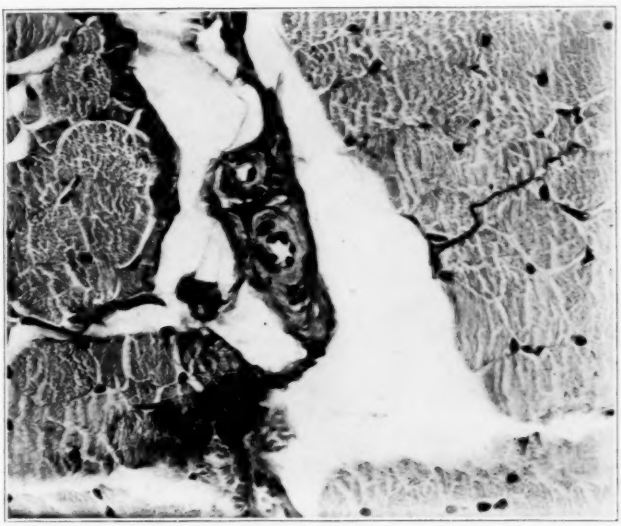

Fig. 2 (case 38).—An arteriole from pectoralis major muscle obtained at biopsy from a child, aged 8. The hypertrophied musculature of the media and the proliferation of the endothelial cells of the intima may be noted. The ratio of thickness of wall to width of lumen, which normally is 1:2, is much upset here. Van Gieson stain; × 350.

although it might possibly produce some hypertrophy of the media. Occlusion of a vessel at a higher level might possibly bring about proliferation of the lining endothelial cells even to the point of occlusion, but evidence is lacking that such occlusion existed in any of these cases. The fundamental changes occurring in these vessels were hypertrophy of the media and proliferation of the intima. There was no degenerative change, nor any change that could be attributed to senile retrogression (figs. 2, 3, 4, 5, 6 and 7).

Fig. 3 (case 38).—An arteriole from pectoralis major muscle obtained at biopsy, showing hypertrophied wall and narrow lumen with an upset ratio of lumen to wall. Van Gieson stain; × 350.

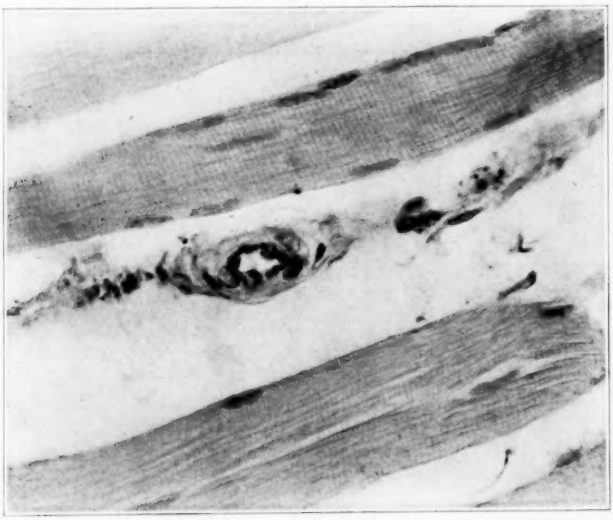

Fig. 4 (case 48).—A small arteriole from pectoralis major muscle obtained at biopsy. The much hypertrophied internal elastic lamina may be noted. Normally, in a vessel of this size, this elastic lamina is extremely slight. The vessel is 29 microns in diameter. Weigert elastic stain; × 475.

In the endeavor to estimate the degree of hypertrophy of the walls of the arterioles and the degree of obstruction produced by the hypertrophy of the media and proliferation of the intima, the most satisfactory method was to measure the thickness of the wall and the diameter of the lumen, and to estimate the ratio of the one to the other. Such measurements had been attempted by Gull and Sutton and by Ewald. However, as stated previously, their histologic specimens were not prepared according to the usual modern technic; the figures they obtained, therefore, cannot be compared with those of the present study. Since normal arterioles had never been measured in this manner, it was necessary to obtain a series of normal controls; therefore, fifty control cases

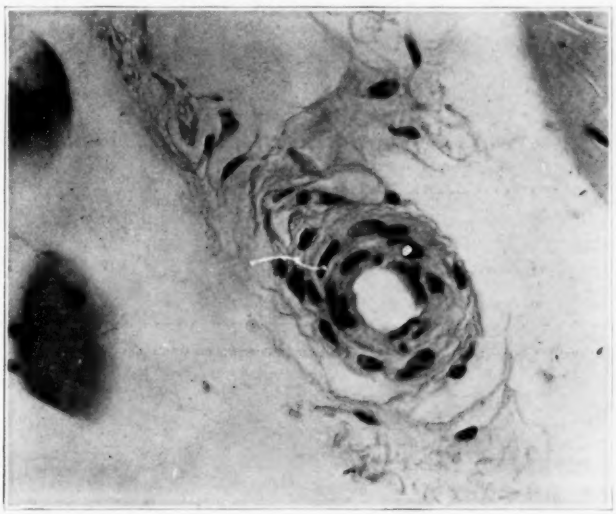

Fig. 5 (case 48).—An arteriole from pectoralis major muscle obtained at biopsy. The thickness of the wall due to hypertrophy of the media and increase in number of nuclei in the musculature may be noted. Hematoxylin and eosin stain; × 475.

were examined. The Bausch and Lomb micrometer was used and only vessels cut at right angles to their course were measured. Figure 8 shows diagrammatically the method of determining the ratio of wall to lumen. The distances *a-b*, *c-d*, *e-f*, and *g-h* were added and divided by four, giving the average for the vessel wall; the distances *b-c* and *f-g* were added and divided by two, giving the average for the lumen. Such estimations were made on several arterioles in each specimen of muscle and the average ratio was taken.

Such measurements of the arterioles show that in the normal one the average ratio of vessel wall to lumen is 1:2, with variations from

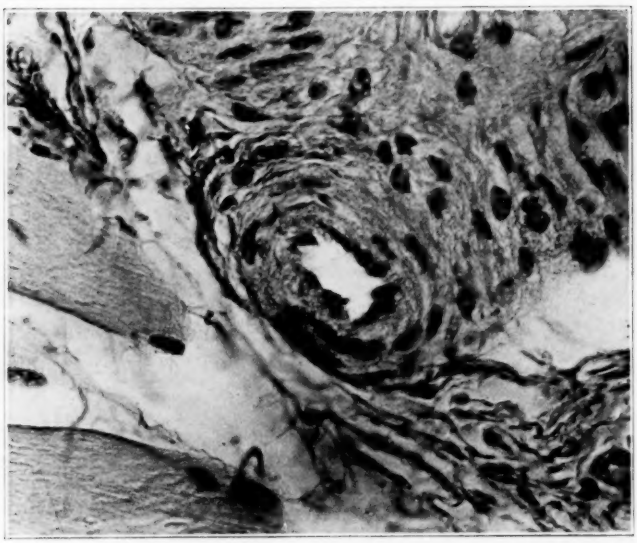

Fig. 6 (case 40).—An arteriole from pectoralis major muscle obtained at biopsy, showing thickening of muscle tissue in media, due to hypertrophy, with increase in number of nuclei. Hyperplasia of the endothelial cells in the intima may also be noted. The vessel wall is almost as thick as the lumen is wide. Van Gieson stain; × 350.

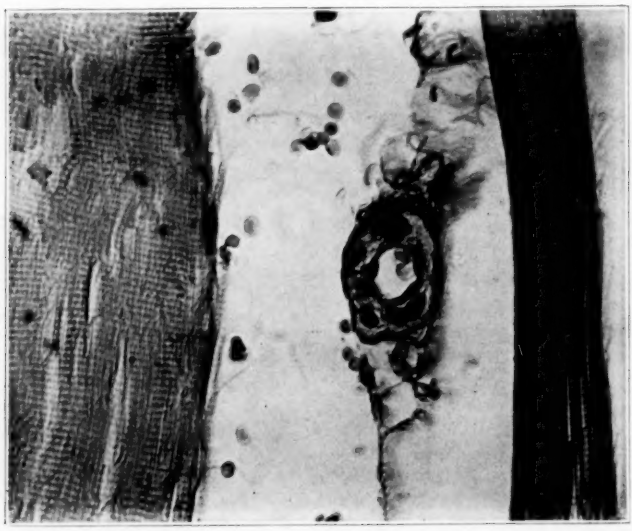

Fig. 7 (case 46).—An arteriole from pectoralis major muscle obtained at biopsy. There is increase in the number of nuclei of the media. There is definite thickening of the media, with hypertrophy. The normal 2:1 ratio of lumen to wall is upset. There is no fibrosis or necrosis in the media. Van Gieson stain; × 350.

1 : 1.7 to 1 : 2.7.[30] In our cases of benign hypertension, the average ratio was 1 : 1.4, with variations from 1 : 1.1 to 1 : 1.8; cases of severe benign or early malignant, and malignant hypertension show practically the same, an average ratio of wall to lumen of 1 : 1.1, with variations from 1 : 0.9 to 1 : 1.7. The figures indicate that, in spite of some overlapping, there is a definite difference between the average ratio obtained for arterioles in the normal states and the average ratio obtained for them in benign and malignant hypertension. It should be pointed out that it seems impossible with this measurement of the arterioles to distinguish the severe benign or early malignant group from that of malignant hypertension (table 1 and fig. 9).

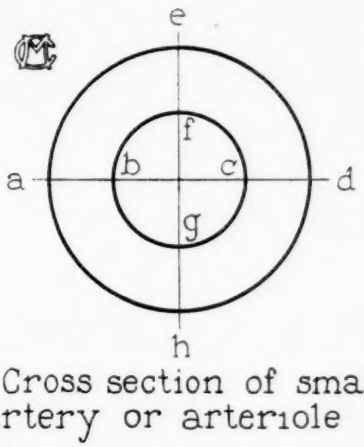

Fig. 8.—A method of determining the ratio of wall to lumen in arterioles.

It is of interest, however, that in only five of the thirty-four cases with a wall-to-lumen ratio of 1 : 1.2 or less was the maximal diastolic pressure less than 140 mm.

Necropsy.—In two cases of malignant hypertension (cases 40 and 46), necropsies were performed two and four months after the biopsies. A summary of the clinical data and of the gross and histologic changes follows (figs. 10, 11, 12, 13, 14 and 15).

Case 40.—A man, aged 23, entered the hospital, Oct. 29, 1927; he had suffered from a sudden paralysis eight days before. He had had frontal headaches and occasionally epistaxis from ten to twelve years previously. Hypertension had been discovered seven years before. Eight days before admission, he had been knocked

30. In case 53, one of chronic glomerulonephritis, the ratio was normal, 1 : 1.8. Biopsy at the time of writing was being carried out in a series of such cases.

from the seat of a truck, and after driving the truck home, he had walked into the house, lain down and become irrational. Right hemiplegia had occurred. There had been some improvement after a few days.

General examination disclosed right hemiplegia. The blood pressure was 190 systolic and 145 diastolic. There was retinitis, grade 2, stage 2 to 3 of malignant hypertension type. The heart was enlarged (grade 1) as revealed by roentgen ray. There were inverted T waves in leads I and II of the electrocardiogram with a questionable coronary T wave in leads I and II. Examination of the urine gave negative results. The phenolsulphonphthalein test of renal function gave a return of dye of 50 per cent, and the blood urea was 40 mg. for each hundred cubic centimeters. The Wassermann reaction of the blood was strongly positive, as was also the Kolmer modification of the Wassermann reaction of the spinal fluid.

The patient received one course of antisyphilitic treatment and returned home slightly improved. He continued treatment at home, the hemiplegia gradually

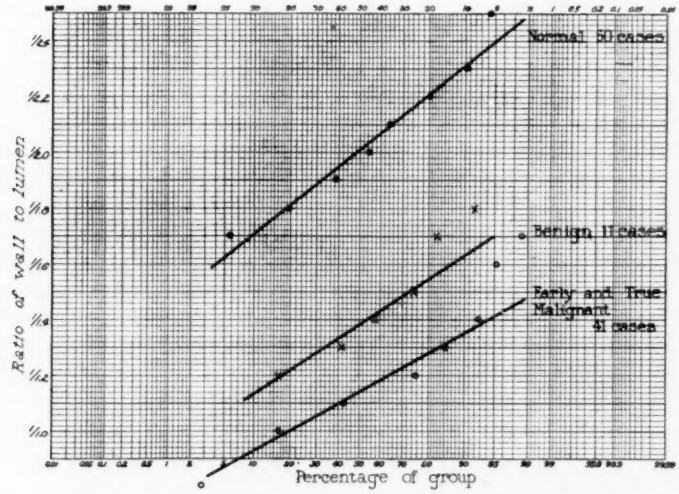

Fig. 9.—Three curves plotted on arithmetic probability paper. The ratios of the walls to the lumen of the arterioles are plotted as ordinates against the percentage number of cases as abscissas. The lower ratios may be noted particularly in the early and true malignant groups.

became less noticeable and he came back, April 23, 1928, for another course of treatment. At this time the blood pressure was 250 systolic and 175 diastolic, the heart was enlarged to grade 2, and there were signs of residual right hemiplegia. Blood urea was 54 mg. for each hundred cubic centimeters. On April 27, 1928, the patient died from cerebral hemorrhage following convulsions. The urine obtained from the bladder at necropsy contained albumin, grade 4, and red blood cells.

The clinical diagnosis was malignant hypertension, cerebral hemorrhage and tertiary syphilis involving the central nervous system (vascular type).

Examination from the standpoint of gross pathologic anatomy revealed atrophy of the muscles of the right forearm and leg and a heart weighing 474 Gm. (normal 300 Gm.). There were moderately large subendothelial hemorrhages

in the left ventricle of the heart. The right coronary and noncoronary cusps of the aortic valve were bound together by firm fibrous adhesions for a distance of about 3 cm. The commissure was thickened and a fibrous band, 3 mm. in diameter, extended up the aorta for a distance of 1 cm. to a point at which it gradually blended into the intima of the aorta. In the remainder of the aorta there was arteriosclerosis, grade 1. The lungs, spleen, liver, gallbladder and bile ducts, stomach, pancreas, bladder, prostate, testes, trachea, thyroid gland, thymus and esophagus appeared normal. The kidneys weighed 145 and 188 Gm., respectively, but except for accentuated fetal lobulations, they appeared grossly normal. The brain externally appeared normal, but on section both lateral ventricles were dilated to grade 3, and were filled with partially clotted blood. There was a hemorrhage in the substance of the brain in the region of the right basal nuclei and an old infarct in the left lenticular nucleus.

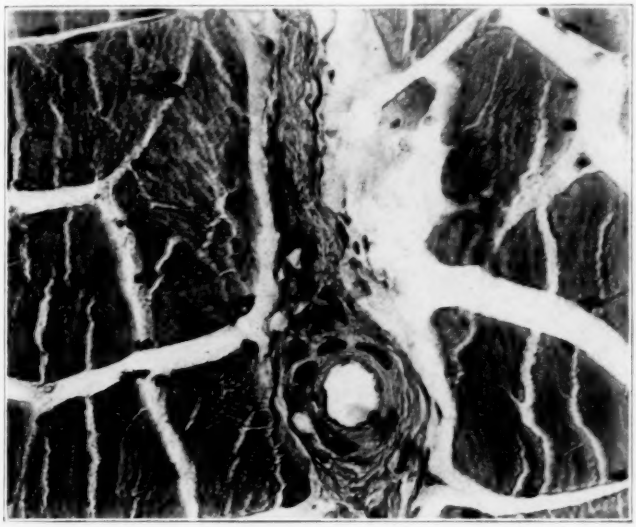

Fig. 10 (case 40).—An arteriole in pectoralis major muscle obtained at necropsy. Changes similar to those described in muscle obtained at biopsy (fig. 6) may be noted. There is proliferation of endothelial cells of the intima; the number of nuclei in the media may be noted. Van Gieson stain; × 350.

On histologic examination, the thyroid gland and the lungs were found to be essentially normal. In sections of the myocardium, liver, pancreas, suprarenal glands, prostate gland, testes and epididymis there were no changes except a slight but definite increase in the thickness of the walls of the arterioles. The trabeculae of the spleen were prominent and the walls of the arterioles were markedly thickened. There was irregular thickening of the walls of the arteries of medium size, suggesting organized mural thrombi.

Numerous sections of the kidneys showed them to be remarkably normal. There was partial or complete hyalinization of a few glomeruli; the remainder were normal. The tubules appeared normal. The walls of the arterioles were definitely but not markedly thickened (figs. 11 and 12). In a section of the wall of the

ascending aorta were diffuse perivascular collections of lymphocytes around the vasa vasorum of the adventitia. Sections through the old infarct in the left lenticular nucleus showed degenerative changes in the nerve cells and diffuse glial proliferation. There was marked thickening of the walls of all the arterioles. Indefinite, patchy, acute degeneration with numerous areas of hemorrhage was found in the right basal ganglions, and the walls of the arterioles here and in the frontal lobe were only slightly thickened. There was no evidence of perivascular lymphocytic collections in any of the sections.

The anatomic diagnosis was malignant hypertension with cardiac hypertrophy; cerebral hemorrhage into the basal nuclei and ventricles; old infarct of the left lenticular nucleus; syphilis of the central nervous system (vascular type) syphilitic aortitis with cohesion of the aortic cusps and subendocardial hemorrhage of the left ventricle.

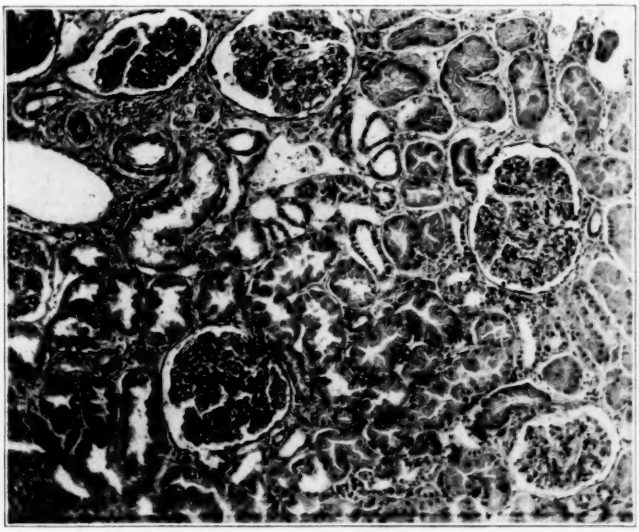

Fig. 11 (case 40).—Cortex of kidney obtained at necropsy. Glomeruli and tubules appear normal. There is a small amount of fibrosis around the small arteries, which have definitely thickened walls. Hematoxylin and eosin stain; × 75.

Case 46.—A man, aged 33, came to the clinic in April, 1913, with a sacro-iliac strain. The systolic blood pressure at that time was 125. He returned three years later for appendectomy. On March 10, 1928, he came complaining of having had, for two and a half years, severe morning headaches, often associated with vomiting and nocturia. At the onset of the headaches, the systolic blood pressure was 160. For the six months previous to admission, he had had dyspnea on exertion, with a sense of constriction in the chest, and aching in the precordium. For two months, he had had a sharp epigastric pain after exertion.

On examination, the transverse diameter of the heart measured 14 cm.; the aortic second sound was accentuated. There was peripheral sclerosis, grade 3.

The edge of the liver was palpable. The blood pressure was 210 systolic and 150 diastolic. There was albuminuria, grade 3, with hyaline and granular casts. The erythrocyte count was normal; hemoglobin was 73 per cent. The phenolsulphonphthalein test of renal function gave a return of dye of 30 per cent, and the blood urea was 60 mg. in each hundred cubic centimeters. There were inverted T waves in leads I and II of the electrocardiogram. There was sclerosis of the retinal arteries, grade 3, and retinitis of the malignant hypertension type with edema of the disks of 2 diopters. Examination of capillaries at the nailfold revealed swift flow in moderately contracted, tortuous vessels.

The patient was sent home with directions to use a diet low in protein and in salt, but he returned, May 13, 1928, because of gastric distress, anorexia, nausea and vomiting. For three days, he had been orthopneic. There had been no edema

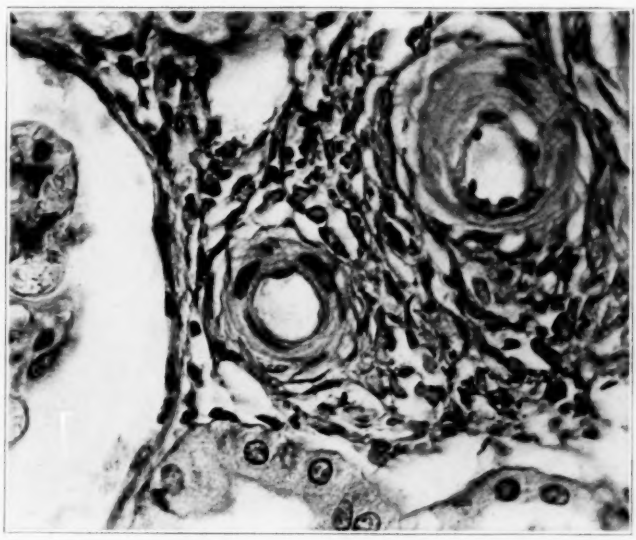

Fig. 12 (case 40).—Arterioles from kidney obtained at necropsy. Thickening of the wall, especially of the tissue of the media, may be noted. One vessel shows areas of so-called necrosis. Van Gieson stain; × 350.

and but slight hemoptysis. He had suffered also from some oliguria and blurring of vision.

On examination, the patient was orthopneic and his breath had an odor that suggested the presence of uremia. The heart was enlarged to grade 3. The blood pressure was 245 systolic and 150 diastolic. The fundus presented the same picture as before, but in addition there were generalized retinal edema, cotton wool exudates and hemorrhages. Hemoglobin was 40 per cent. There was albuminuria, grade 2. The blood urea was 274 mg., and creatinine 12.2 mg. for each hundred cubic centimeters. The patient's condition progressively grew worse and he died nine days later. Signs of acute pericarditis, Cheyne-Stokes respiration and coma had developed. The blood urea in these last days rose to 561 mg., and the blood creatinine to 27.2 mg. in each hundred cubic centimeters.

The clinical diagnosis was malignant hypertension, chronic myocardial degeneration (decompensated), acute pericarditis, general and renal sclerosis of the arteries and arterioles, and uremia.

Examination for features of gross pathologic anatomy did not reveal edema, although the peritoneal cavity contained 50 cc. of clear, straw-colored fluid. Both pleural cavities were practically obliterated by fibrous adhesions. The pericardial cavity contained 100 cc. of cloudy, brown fluid, in which were flakes of fibrin. The heart weighed 618 Gm. On both visceral and parietal pericardial surfaces were roughened, hyperemic areas, covered with thin layers of soft exudate. There was sclerosis of the coronary arteries, grade 2. The left ventricle was dilated to grade 2. The valves and myocardium appeared normal. The aorta showed evidence of arteriosclerosis, grade 1. There was emphysema, grade 2, in the apexes of both lungs. In the right upper lobe near the hilum were two small caseating tubercles. The large bronchi of the right lung were hyperemic and were filled with mucopurulent material. In some places there were slight saccular dilatations. Bilaterally there was tuberculous caseation and calcification of the hilar lymph nodes. There was slight, old perisplenitis. The liver weighed 1,900 Gm. and was chocolate-colored, and cut sections had a typical nutmeg appearance. The gallbladder and biliary tracts, the stomach, pancreas, intestines and suprarenal glands appeared normal. The kidneys weighed, respectively, 125 and 118 Gm. Their surfaces were granular, mottled and pinkish-gray and had numerous punctate hemorrhages. The cut surface was pale, markings were obliterated and there were numerous punctate hemorrhages. There was definite, symmetrical atrophy of both cortex and medulla and the corticomedullary vessels were prominent and gaped. There was noticeable hypertrophy of the wall of the main renal artery. The median lobe of the prostate was slightly enlarged.

On histologic examination, sections of the prostate and thyroid glands were essentially normal. The walls of the arterioles of the pancreas, suprarenal glands, spleen and stomach were definitely thickened. There was, also, moderate congestion in the spleen. There was a small leiomyoma in the wall and a polyp of the stomach. There was some diffuse atrophy of the hepatic cells, which contained a fair amount of finely divided fat, particularly those in the central zones. The lungs were normal, except for active tuberculosis in the margins of one of the caseating tubercles. In the heart there was definite proliferation of the epicardial endothelium and there were scattered lymphocytes through the subepicardial fat. On the surface of the endothelium was a loosely adherent, amorphous acellular exudate. There was some variation in the size and shape of the nuclei of the muscle fibers and the fibers were more than normally spread apart by loose fibrous tissue. There was definite uniform thickening of the walls of the coronary arterioles. Sections stained for fat were negative. In the kidney, at least 60 per cent of the glomeruli appeared normal, except for some contraction and atrophy of the tufts. About 30 per cent were completely hyalinized. In the remainder were varying degrees of hyaline fibrosis, adhesions of tuft to capsule and, in one or two, weak attempts at capsular epithelial proliferation. In a few, the capsular spaces were filled with blood. There were extreme changes in the tubules; most of them were atrophied and constricted. Some were dilated and contained much hyaline material and débris. Many had been completely destroyed, and many contained considerable fat. There was a marked diffuse increase of rather acellular, fibrous interstitial tissue, with a few large areas of hemorrhage and a few small infarcts. The medium-sized and smaller arterioles were prominent and tortuous. In their walls was an extreme degree of thickening, proliferation and fibrosis, with marked splitting of the internal elastic laminae, and in many places the lumen was so constricted as to be barely visible (figs. 14 and 15).

The anatomic diagnosis was malignant hypertension with sclerotic atrophy of the arterioles of the kidneys and cardiac hypertrophy; acute fibrinous pericarditis; dilatation, grade 2, of the left cardiac ventricle; benign prostatic hypertrophy, grade 1; healed and active tuberculosis of the pleura, lungs and hilar lymph nodes, and acute purulent bronchitis.

Detailed histologic study and measurements of the peripheral arterioles in various tissues of these two cases revealed practically the same change both in the structure of the vessels and in the ratio of vessel wall to lumen, as observed in the previous biopsy (figs. 6, 7, 10 and 13). The arterioles in the kidney (figs. 12 and 15) were more extensively and seriously involved than vessels elsewhere. Some of them were almost

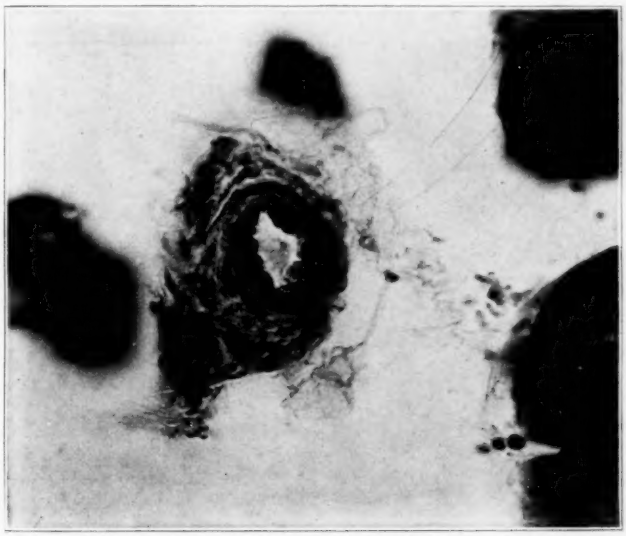

Fig. 13 (case 46).—An arteriole in pectoralis major muscle obtained at necropsy. The changes are similar to those seen in the muscle obtained by biopsy. Hematoxylin and eosin stain; × 350.

completely occluded. In case 40 (fig. 11), the glomeruli were well preserved, and there was no glomerulonephritis, whereas in case 46 (fig. 14) there were early fibrosis and atrophy of glomeruli, and many tubules had been destroyed. This picture has been termed by Ellis [31] secondary ischemic nephritis. Some of the small arteries and some arterioles showed evidence of the so-called necrosis of the media that has been described by Fahr [12] and others [32] (fig. 15). It seems to us that this could be

31. Ellis, Arthur, quoted by Brain, R. T., and Kay, H. D.: A New Test of Renal Function, Quart J. Med. **22**:203, 1929.

32. Herxheimer (footnote 10). Stern (footnote 11).

explained on the basis of ischemia rather than on that of the presence of a specific toxin. The blood supply to such vessels is supposed by many to come from the lumen and if, after marked hypertrophy with subsequent narrowing of the lumen, the blood supply is inadequate, ischemia, with fatty changes and necrosis, readily may follow.

COMMENT

The results of this study indicate that associated with hypertension a diffuse disturbance of the arterial side of the vascular system exists both clinically and histologically in varying degrees of severity.

In benign hypertension there may be no lesions in the peripheral arterioles or there may be moderate ones. Allbutt [33] considered dynamic

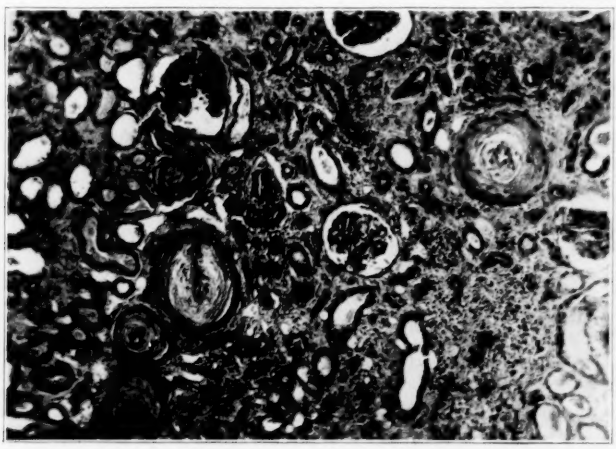

Fig. 14 (case 46).—Cortex of kidney obtained at necropsy. Extreme thickening of arterioles may be seen and marked increase in the interstitial connective tissue. The glomeruli show early fibrosis and atrophy, and many tubules have been destroyed. Hematoxylin and eosin stain; × 75.

narrowing, rather than organic changes in the arterioles, as the primary lesion. Our data, obtained at biopsy, are in harmony with the long retention of adequate retinal, cardiac and renal function and with the stationary or slow progression of the general condition. In the second group of cases, those of severe benign or early malignant hypertension, the clinical observations indicate more serious involvement. The blood pressure generally is higher; retinal and palpable peripheral arteriosclerosis is more marked; distinct, although often slight, abnormalities in the

33. Allbutt, C.: Senile Plethora or High Arterial Pressure in Elderly Persons, Tr. Hunterian Soc., 1895-1896, p. 38.

electrocardiogram and the renal function are more frequently present. In spite of these clinical evidences of diffuse involvement, and a corresponding marked pathologic change in the peripheral arterioles that often is present, many of these patients still have remarkably good retinal, cardiac and renal function. Such results suggest that either the lesion in the arteriole, although marked, has been of shorter duration, or better compensation has taken place. In our cases of malignant hypertension there has been a definite type of retinitis. Cardiac enlargement and early disturbances of cardiac and renal function are more often present than in either of the other groups. The blood pressure usually is high, but

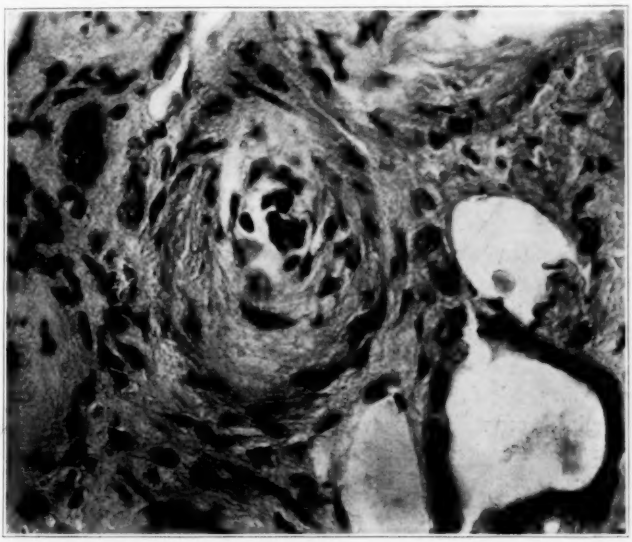

Fig. 15 (case 46).—A small artery in the kidney, obtained at necropsy. The lumen is almost obliterated, and thickening of the wall is extreme. There is proliferation of endothelial cells of the intima. The number of cells in the musculature of the media and the area of necrosis which may be ischemic in origin may be noted. Hematoxylin and eosin stain; × 350.

we have seen a few instances in which the blood pressure was only moderately increased, yet other features of the syndrome were present. There is almost invariably a marked thickening of the wall and narrowing of the lumen of the arteriole in muscles. The clinical course is rapidly progressive. In other words, there are good reasons for considering malignant hypertension as the terminal stage of the severe benign or early malignant type. We also have seen cases which undoubtedly belong to the benign group but which, at a later date, present the classic fea-

tures of the malignant type. Thus, there is clinical and pathologic evidence, in certain instances, at least, that the basic lesion in the three groups is one of degree. On the other hand, we recognize that in the great majority of cases of benign hypertension, the malignant syndrome never develops. In consideration of these facts, any possible theory as to the cause of diffuse vascular hypertensive disease must explain: (1) the slow progression in benign hypertension; (2) the rapid development and course of malignant hypertension, particularly in the young; (3) the gradual transition from the cleancut picture of benign to that of malignant hypertension, and (4) the occasional development of malignant hypertension in cases of chronic glomerulonephritis.

When a lesion was present in the arterioles of voluntary muscle, the chief pathologic changes were hypertrophy of the media, proliferation of the intima and marked reduction in the ratio of wall to lumen. There were no actual signs of degeneration or changes similar to those of senile retrogression. The facts that certain lesions were found in the arterioles of muscle obtained during life, and that later, at necropsy of the same patients, identical lesions were found and that similar lesions also were present in the arterioles of many organs afford significant evidence that the changes observed in arterioles of muscles are indicative of diffuse vascular disease. The lesion, if progressive, also offers a possible explanation of the widespread focal lesions seen at necropsy in cases of malignant hypertension. In our experience, the presence or absence of this lesion in the arterioles of muscles may determine the diagnosis and prognosis in the individual case. The frequent absence of any lesion in the arterioles of voluntary muscle obtained at necropsy in cases of essential hypertension, as reported by Jores,[5] Fahr,[12] Evans [13] and Fishberg,[14] seems best explained by the fact that their series, perhaps, did not include cases of the serious progressive type of hypertension, such as those which we have classed as cases of early malignant or malignant hypertension.

The type of lesion in the arteriole suggests hypertrophy in the face of excessive strain. One interpretation would be that the lesion is secondary to the hypertension. However, there are cases of malignant hypertension in which there is only a moderate rise in blood pressure; this might indicate that the diffuse involvement of the arterioles is primary, and that sustained hypertension might result on account of increased peripheral resistance. More facts are needed to explain the mechanism of the intricate balance between the output of the heart and the changes in the peripheral vascular structures.

The ophthalmoscopic observations of Wagener [34] in certain cases of this series are of great interest. He noted occasionally in the absence of

34. Wagener, H. P.: Personal communication to the author.

definite sclerosis a marked narrowing of the small retinal arteries, which was due to actual vasoconstriction; later these same arteries showed evident sclerosis of their walls. This observation suggests that marked, continuous vasoconstriction may precede and later may give rise to demonstrable histologic change in the arterioles. The uniform occurrence of hypertrophy in the circular muscular layer of the arteriole lends support to such a theory of development.

Certain physiologic and clinical observations on the capillaries have a possible bearing on this point. Richards and Schmidt,[35] from direct observation of the vessels of the kidney of the frog, observed that the slitlike opening at the juncture of the afferent glomerular arterioles and the glomerular capillaries is especially susceptible to constrictor influence. These authors also observed a similar phenomenon in the arterioles in the muscle of the frog. Landis,[27] in his micropressure determinations in the mesentery of the frog, noted a sharp reduction in pulse pressure at the arteriole-capillary juncture, and suggested that this fall may be partly due to similar narrow openings at the points where the capillaries spring from arterioles. Brown and Roth [36] suggested that the fast, spurting or jerky flow seen in the capillaries at the nailfold in many cases of hypertension may be due to a possible disturbance of the precapillary arterioles, an intermittent closure of the vessels. They believed that this periodic closure may be a factor in the production of increased peripheral resistance.

The primary cause of diffuse hypertensive vascular disease is still mysterious. Syphilis is so rarely present that it does not seem to be a factor. It is difficult to accept the conclusion of Fahr that the hypertension in all cases is of renal origin. Two general possibilities seem more probable. Hypertension, it seems, may be due to an inherent disturbance of the sympathetic nervous system or it may be due to the action of a hypothetic pressor substance on the sympathetic chain, on sympathetic endings in the wall of the arteriole or directly on the smooth muscle of the vessel wall.

SUMMARY

The arterioles in voluntary muscle of ambulatory patients with diffuse hypertensive vascular disease frequently show distinctive histologic changes. These changes differ in degree and may afford a valuable index for predicting the ultimate outcome in the individual case.

35. Richards, A. N., and Schmidt, C. F.: A Description of the Glomerular Circulation in the Frog's Kidney and Observations Concerning the Action of Adrenalin and Various Other Substances upon It, Am. J. Physiol. **71**:178, 1924-1925.

36. Brown, G. E., and Roth, G. M.: Biomicroscopy of the Surface Capillaries in Normal and Pathologic Subjects, M. J. Australia **1**:499, 1927.

PROLONGATION OF THE LIFE OF NEPHRECTOMIZED DOGS

WITH THE PRODUCTION OF EDEMA *

E. E. LYON, M.S.

A. L. SHAFTON, M.S.

AND

A. C. IVY, M.D.

WITH THE ASSISTANCE OF F. S. BARRY

CHICAGO

The object of this research was to determine by what means life could be prolonged most effectively following double nephrectomy and to study the effect of these methods on the blood chemistry and resulting symptoms.

Vicarious elimination has been suggested as the means by which substances usually eliminated by the kidneys may be secreted or excreted by the stomach, intestines, saliva, sweat and lungs.[1]

Working on the theory that stimulation of those processes and organs which carry on vicarious elimination would result in a decreased retention of nitrogenous waste products and would prevent the absorption of toxic products from the intestines and thus prolong life, we studied the effects on nephrectomized dogs of procedures designed to increase the secretory and excretory activity of the gastro-intestinal tract.

LITERATURE

Brown-Séquard, in 1889, published his theory on internal secretions, in which the kidney was included as one of the organs of internal secretion, ascribing uremia to the failure or lack of such a secretion. In 1893,[2] he stated that while nephrectomized animals lived only thirty hours on the average, similar animals to which kidney extracts were given lived sixty hours. He concluded that the accumulation of the nitrogenous waste products was not the only factor responsible for the appearance of uremic symptoms, the disturbance of the internal secretion of the kidney being a more powerful and active factor.

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* From the Department of Physiology and Pharmacology, Northwestern University School.

1. McEnery, E. T.; Meyer, Jacob, and Ivy, A. C.: J. Lab. & Clin. Med. **12**:368, 1927.

2. Brown-Séquard: Arch. d. phys. norm. et path. **5**:778, 1893.

Herter and Wakeman[3] reported a study of the alterations in the composition of the blood resulting from double nephrectomy. They used dogs in most instances and removed both kidneys at one operation. They noted that these dogs developed a loss of appetite, drowsiness, vomiting, diarrhea and lowering of temperature. In a few instances, the second kidney was removed several days after the removal of the first. In a few others both ureters were ligated and the kidneys not removed. All the animals were bled about the time of impending death. Their investigations revealed that the alkalinity of the blood was increased; that the blood urea was increased to ten times the normal value in eighty-two hours or less; that the uric acid content of the blood was not increased, and that the alcoholic and etherial extractives were increased. Eighteen dogs lived from twenty-two to eighty-two hours following double nephrectomy, the average being forty-eight hours. Six dogs lived from thirty-six to seventy-two hours following ligation of both ureters, the average being fifty hours. The blood urea in the nephrectomized animals varied from 103 to 458 mg. per hundred cubic centimeters, the average being 315 mg. The tissues contained from four to five times more than the normal percentage of nitrogen, probably urea. This early work is open to criticism because of the great inaccuracy of the analytic methods employed.

Bradford,[4] in 1899, in a study of the kidney and metabolism, made a few observations on the results of double nephrectomy and ligature of both ureters. Of four animals in which both ureters had been ligated, two were bled to death seventy-two hours after the operation, and two were found dead on the morning of the third day, so that they lived between forty-eight and sixty hours. A double nephrectomy was performed in only one animal and this animal was bled to death seventy-two hours after the operation.

Vitzou,[5] in 1902, investigating the internal secretion of the kidney, claimed to have kept animals alive following a two-stage double nephrectomy for as high as from 146 to 164 hours by no other measure than injection of blood serum from renal veins of healthy animals of the same species. This he interpreted as due to the internal secretion of the kidneys.

Amos,[6] in 1905, pointed out a definite variability in the tolerance of different species of animals to renal intoxication. He found that guinea-pigs, after unilateral ureteral obstruction, lived for an average of nineteen and one-half days, whereas rats, under the same conditions,

3. Herter and Wakeman: J. Exper. Med. **4**:117, 1899.
4. Bradford, J. R.: J. Physiol. **23**:415, 1899.
5. Vitzou, A. N.: Bucharest, 1902.
6. Amos, B.: J. Path. & Bact. **10**:265, 1905.

lived for an average of fifty-two days; but in each species, when both ureters were simultaneously ligated, the animal died in two days.

In the experiments of Ajello and Parascandalo, as quoted by Pearce,[7] twelve control dogs died in from four to forty-eight hours after double nephrectomy with symptoms of dyspnea, convulsions and gastro-intestinal disturbances considered to be uremic; while of ten nephrectomized dogs treated with glycerin extracts of kidney substance, one lived four days, six lived three days, and three died in from forty-eight to fifty-two hours. Many other investigations give similar results.

While studying the effects of reduction of the kidney substance, Karsner, Bunker and Grabfield [8] noted that following the removal of the total kidney substance the urea nitrogen content of the blood increased until death intervened. The average length of life following total nephrectomy in three dogs was seventy-six hours; one dog lived ninety-six hours. The average urea nitrogen content of the blood was 285 mg. per hundred cubic centimeters.

In 1921, Foster [9] noted that in nephrectomized dogs the urea formed 60 per cent or more of the total nonprotein nitrogen; while in uremia it seldom formed more than 65 per cent and often less than 50 per cent of the total nonprotein nitrogen.

Wallace and Pellini [10] observed that double nephrectomy failed to produce acidosis. They made their observations on two dogs, both of which lived four days following the operation.

Allen, Scharf and Lunden,[11] in a report of a study of experimental nephritis, stated: "Total nephrectomy produces a condition which in dogs is acutely fatal, generally within a couple of days. Nitrogen retention and acidosis are demonstrable, but death occurs from weakness without edema, hypertension or any of the clinical phenomena of nephritis. The same procedure when carried out in goats yielded better results, these animals surviving total nephrectomy for two weeks." They could not produce edema even in partially nephrectomized dogs with the heaviest feeding of salt.

Putaszek [12] recently reported that he was unable to obtain very marked symptoms of acid intoxication in dogs surviving from two to

7. Pearce, R. M.: The Theory of Chemical Correlation as Applied to the Pathology of the Kidney, Arch. Int. Med. **2**:77 (Aug.) 1908.

8. Karsner; Bunker, and Grabfield: J. Exper. Med. **22**:544, 1915.

9. Foster, N. B.: Uremia, J. A. M. A. **76**:28 (Jan. 29) 1921.

10. Wallace, G. B., and Pellini, E. J.: Capillary Poisons and Acidosis, Arch. Int. Med. **28**:711 (Dec.) 1921.

11. Allen, F. M.; Scharf, F., and Lunden, H.: Clinical and Experimental Renal Deficiency, J. A. M. A. **85**:1698 (Nov. 28) 1925.

12. Putaszek, L.: Compt. rend. Soc. de biol. **96**:567, 1927.

five days after double nephrectomy. There was a small diminution in alkali reserve, but the slight decrease was in marked contrast to the fall observed in cases of human uremia. He expressed the opinion that when the kidneys are extirpated, some extrarenal mechanism maintains the alkali reserve approximately normal, whereas in uremia, the extrarenal mechanism breaks down along with the kidneys.

Andrews [13] reported several cases of dogs surviving from four to ten days following total nephrectomy. The animals did not show evidences of acid intoxication even in the terminal stages. They were active, played about and had good appetites. He injected hypertonic salt solution in such amounts that the chloride content of the blood was comparable to that in uremia, and reproduced every manifestation of uremia seen in the human being. Both the chloride and the water rapidly made their way from the blood into the tissues; the brain and liver showed the highest chloride content and were the organs chiefly involved. He assumed that degenerative changes in the liver due to an increased sodium-calcium content are the fundamental sources of the uremic toxins.

Swingle [14] recently reported a study of the acid-base equilibrium after bilateral nephrectomy. He employed a two-stage operation and reported eight dogs with an average postoperative life of eighty-five hours, the longest being 120 and the shortest sixty-six hours. He stated that although a slight fall in alkali reserve may occur, the animals do not develop acid intoxication. He found retention of sulphate, phosphate and urea, and a diminution of blood chlorides. He felt that the decrease in chlorides which occurred was not due to chlorides lost in the vomitus, because one of the dogs did not vomit.

From these investigations it is seen that the length of life following total nephrectomy is extremely variable. The average length of life in these animals is about seventy-two hours. The extremely low figures on survival time, of from four to twenty-four hours, must have been due to operative procedure. The earlier investigations of the alterations of the composition of the blood resulting from double nephrectomy are open to criticism because of the methods of analysis employed at that time.

EXPERIMENTAL METHODS

Large, well nourished dogs, averaging in weight about 18 Kg., were employed as experimental animals. These animals were specially selected, being in the best physical condition; the smaller dogs were rejected because it was our experience, as well as that of others, that the larger and more vigorous animals survive bilateral nephrectomy longer than the smaller dogs. They were kept in the laboratory several days before using in order to accustom them to their new sur-

13. Andrews, E.: Experimental Uremia, Arch. Int. Med. **40**:548 (Oct.) 1927.
14. Swingle, W. W.: Am. J. Physiol. **86**:450, 1928.

roundings and to obtain the normal blood chemistry values. In all cases, except groups II and IX, the animals were fed raw ground meat mixed with bread.

The animals in groups II and IX were fed 200 Gm. of bread, 500 cc. of milk, and from 100 to 150 Gm. of lactose each day before operation until they developed diarrhea. After operation this diet was continued by forced feeding when necessary in group II. But the animals in group IX were allowed to go without food when they refused it. Specimens of blood were drawn from the saphenous vein by the use of a syringe.

Both kidneys were removed in one operation. Through a midline incision, after severing of the peritoneal fold at the upper pole of the kidney, the kidney was delivered and decapsulated. The renal vessels were clamped, doubly ligated and cut. The ureter was ligated separately and cut. All dogs were given a preoperative injection of ½ grain (8.32 mg.) of morphine sulphate and 1/100 grain (0.6 mg.) of atrophine sulphate. Anesthesia was induced with ether. The period of operation was from fifteen minutes to one-half hour.

The analysis of the blood was performed according to the method of Folin and Wu. A protein-free filtrate was prepared and examined for nonprotein nitrogen, urea nitrogen, creatinine and chlorides.

Group I: The dogs in this group were fed a meat diet, and were used as controls.

Group II: These dogs were put on the lactose diet described, for from seven to ten days before operation, and after operation were fed by tube when they refused to eat.

Group III: Following bilateral nephrectomy the animals in this group, fed a meat diet, were given injections of 2 mg. of histamine subcutaneously, two to three times a day.

Group IV: These animals, also fed a meat diet, were given from 1 to 2 ounces of magnesium sulphate before operation until diarrhea occurred, and following operation, by tube when necessary.

Group V: Following operation, these animals, fed a meat diet, were given a daily intravenous injection of Ringer's solution with increased sodium bicarbonate content. This solution, which we called "sodium bicarbonate Ringer's," was made up as follows: sodium chloride, 0.45 per cent; potassium chloride, 0.42 per cent; calcium chloride, 0.24 per cent, and sodium bicarbonate, 0.65 per cent.

Group VI: The same diet was used in this group. Following operation, the animals were given a daily intravenous injection of Ringer's solution made as follows: sodium chloride, 0.9 per cent; potassium chloride, 0.42 per cent; calcium chloride, 0.24 per cent, and sodium bicarbonate, 0.02 per cent.

Group VII: These animals, fed a meat diet, were given from 1,000 to 1,500 cc. of Ringer's solution subcutaneously, each day, in two or three doses.

Group VIII: A meat diet was used in this group and from 1,000 to 1,500 cc. of bicarbonate Ringer's solution given subcutaneously, each day following operation.

Group IX: Lactose diet was instituted preceding the operation until diarrhea developed. After the operation, from 1,000 to 1,500 cc. of Ringer's solution was given subcutaneously each day.

RESULTS

Group I (tables 1 and 2).—There were six animals in this group, and their average weight was 17.7 Kg. They were kept on a meat diet before operation and for as long after operation as they would eat. In general, they appeared normal for about forty-eight to sixty hours after operation and occasionally for three days. They ate, walked about and

seemed in excellent condition. The first symptoms were "malaise" and loss of appetite. They sniffed at offered food, possibly ate a bite or two and then turned away. Then they became listless, lying quietly for hours at a time, but when aroused, walked about in normal fashion. In this group, vomiting appeared as a rule on the third day, the vomitus consisting of bile stained fluid and mucus. Diarrhea soon set in and in some cases, especially as the end approached, the stools became bloody. As symptoms progressed, the animals showed increased weakness, especially of the hind legs, and swayed from side to side when walking. As the terminal stage approached, the animals passed into increasing stupor, then into coma, and finally died. One of the animals in this group showed marked salivation on the third day. The average length of life following bilateral nephrectomy in this group was 105.6 hours.

Analysis of the blood in these dogs showed a steady, day to day increase in the content of nonprotein nitrogen, urea nitrogen, creatinine, and a reduction of the chlorides. Normally, the ratio of the nonprotein nitrogen to urea nitrogen is usually 2:1, but as these substances accumulate following total nephrectomy the urea nitrogen increases at a greater rate than the nonprotein nitrogen, the ratio becoming 3:2.

Atchley and Benedict [15] observed diminution of the chlorides following bilateral ureteral ligation of dogs. They studied the chlorides lost in the vomitus and excreted in the feces, but they were unable to account for the loss on the basis of vomiting or excessive excretion. Study of chloride concentration of various tissues such as muscle and brain likewise failed to show deviations from the normal. They were unable to account for the fall in blood chlorides on the basis of their examinations.

The results of the daily examination of the blood of one of the dogs in this group are given in table 1.

Table 2 shows the duration of life, analysis of the blood just before death and time of appearance of vomiting and diarrhea of the animals in this group. At autopsy, the chief changes were found in the gastrointestinal tract and liver. The stomach presented a moderate degree of gastritis, and the lower portion of the ileum and colon were moderately inflamed. The liver was dark and congested. The brain was more wet and the cerebral vessels were more congested than normal.

Group II (tables 3 and 4).—There were eleven dogs in this group, and their average weight was 18.7 Kg. They were kept on a low protein lactose diet as described, and when diarrhea had been instituted, bilateral nephrectomy was performed. The average length of life following the operation in this group was 137.6 hours, an average of thirty-two hours longer than the controls. One animal in this group lived 194 hours, which was fifty-four hours longer than any animal in the control group,

15. Atchley, D. W., and Benedict, E. M.: J. Biol. Chem. **73**:1, 1927.

and eighty-eight hours longer than the average for this group. In spite of the great variability in the length of life following total nephrectomy, both in these experiments and in those of other investigators, a comparison of the average length of life of the two groups may be made, because we feel that the groups include a sufficient number of animals.

After removal of both kidneys, the symptoms of latent uremia appeared as in the control animals, but were somewhat delayed.

The analysis of the blood of these dogs showed that the retention of the nitrogenous waste products does not occur as rapidly as in the control animals.

TABLE 1.—*Typical Blood Observations on Control Dog 4, Group I, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Mg. per 100 Cc.	Comment
4/30/26	..	15.2	29.1	21.6	1.1	0.450	
5/ 1/26	..	15.2	29.6	22.4	1.4	0.445	Operation, 12 noon
5/ 2/26	22	14.8	72.2	38.4	3.43	0.431	
5/ 3/26	51	14.7	158.8	100.8	8.5	0.429	Vomited
5/ 4/26	70	14.6	201.6	182.0	10.1	0.387	Anorexia
5/ 5/26	93	14.3	238.0	235.2	12.5	0.412	Drowsy, vomited
5/ 6/26	122	12.8	403.2	257.2	14.7	0.341	Has diarrhea, vomited
5/ 6/26	..	....	.....	.....	....	.....	Died in coma at 2 p. m.

TABLE 2.—*Data on Control Dogs in Group I Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Gm. per 100 Cc.	Vomiting, Hours	Diarrhea, Hours	Salivation, Hours
1.....	140	196.0	126.0	14.8	0.231	73	45	73
2.....	139	366.8	.....	15.0	0.212	98	98	..
3.....	88	196.0	100.0	10.5	0.396	..	72	..
4.....	122	403.2	257.2	14.7	0.311	51	122	..
20.....	60	251.4	127.6	12.1	.....	..	41	..
21.....	85	485.0	241.0	15.7	.....	..	72	..
Average....	105.6	308.2	202.4	13.8	0.290	74	75	..

Note: No edema nor convulsions were observed.

At autopsy, there was usually a more marked inflammation of the stomach and intestinal mucosa than occurred in the control animals, probably because of the longer life. The other changes were essentially the same. The results of the daily examinations of the blood of one of the dogs in this group are given in table 3, while table 4 includes the summary of the results obtained in the series.

Group III (tables 5 and 6).—There were seven animals in this group. Following bilateral nephrectomy, these animals received injections of histamine three times a day.

McEnery, Meyer and Ivy [1] have shown that in experimental nephritis the gastric glands respond to an injection of histamine and that urea is eliminated in the gastric secretions. We used this means of increasing vicarious elimination in this group of animals. And although we were

not successful in prolonging the life of these animals, the average length of life being ninety-eight and seven-tenths hours, the analysis of the blood revealed a definite delay in the retention of the nitrogenous waste products, and following the injections a drop was demonstrated in the content of nonprotein nitrogen, urea nitrogen and creatinine. In dog 47, the analysis of the blood at the fifty-third and the seventy-second hours showed only a slight rise in the creatinine and no increase in the content of nonprotein nitrogen and urea nitrogen over this period of nineteen hours. Another interesting observation in this group was the

TABLE 3.—*Typical Blood Changes in Dog 9, Group II, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Mg. per 100 Cc.	Comment
7/26/26	..	19.5	25.2	14.0	1.5	0.41	Has diarrhea
7/27/26	..	19.5	32.8	13.0	1.5	0.41	Operation at 5 p. m.
7/28/26	14	18.4	56.0	37.2	3.19	0.39	Drank water
7/29/26	48	18.1	87.6	44.8	6.3	0.38	Fed by tube
7/30/26	64	18.1	120.4	104.0	9.0	0.38	
7/31/26	88	17.6	131.6	117.6	9.1	0.37	
8/ 1/26	112	17.2	163.8	124.5	10.5	0.37	
8/ 2/26	139	16.2	204.4	131.6	11.7	0.35	
8/ 3/26	167	15.9	151.2	105.0	13.0	0.35	
8/ 4/26	186	15.2	261.3	143.6	15.8	0.34	Vomiting, stupor; died in coma at 11 a. m.

TABLE 4.—*Data on Dogs in Group II Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Mg. per 100 Cc.	Vomiting, Hours
5	168	236.0	168.2	16.3	0.432	70
7	136	270.0	191.8	11.5	0.209	146
8	194	431.2	408.8	19.8	0.300	..
9	186	261.3	143.6	15.8	.....	..
23	130	360.5	174.5	12.0	.....	23
24	130	306.1	182.5	8.6	.....	44
27	138	208.0	130.4	13.0	0.456	74
33	108	102.5	133.0	11.4	0.312	94
34	145	454.1	386.0	15.3	0.291	115
22	89	254.0	61.5	9.4	.....	25
32	90	240.0	194.0	9.8	0.406	71
Average	137.6	283.8	189.2	12.08	0.217	73

development of convulsions in five of the seven animals. These began with slight muscular twitchings from two to ten hours before death, which increased in severity until definite clonic convulsions of all muscles were noted before death. Three of the animals in this group showed spasmodic contraction of the diaphragm synchronous with the heart beat.

The injection of histamine even in larger doses does not produce such results in normal animals.

The changes found at autopsy in these animals were similar to those observed in the control animals, except that in this group rigor mortis occurred soon after death.

Table 5 shows the results of an hourly analysis of the blood in one of three animals. Table 6 includes each animal in this series.

Group IV (table 7).—In this series there were six animals. They were given 1 or 2 ounces of magnesium sulphate by stomach tube every day before operation until diarrhea developed, and after operation until death. The average length of life in this group was eighty-nine hours.

TABLE 5.—*Data on Dog 47, Group III, Following Nephrectomy*

Date	Hours After Operation	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Comment
2/13/28	0	26.4	14.1	1.70	Meat diet; operation at 1 p. m.
2/16/28	47	122.0	72.0	7.23	Condition fine; ate and drank
	47	.....	.....	....	2 mg. histamine
	48	135.5	98.0	7.89	
	48	.....	.....	....	2 mg. histamine
	49.5	178.5	91.0	9.09	
	53	150.0	112.0	8.57	
2/17/28	72	150.0	112.0	9.6	Condition good
	72	.....	.....	....	2 mg. histamine
	73	146.5	95.2	10.2	
	73	.....	.....	....	2 mg. histamine
	74	189.0	88.0	11.1	
	78	186.0	112.0	10.6	
	81	.....	.....	....	2 mg. histamine
2/18/28	..	.....	.....	....	Spasmodic contraction of diaphragm
2/19/28	117	272.5	217.0	14.6	Condition poor
	117	.....	.....	....	2 mg. histamine
	118	275.0	196.0	15.3	
	118	.....	.....	....	2 mg histamine
	119	267.0	200.0	15.7	
	123	309.0	238.0	15.7	

TABLE 6.—*Data on Dogs in Group III Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Gm. per 100 Cc.	Vomiting, Hours	Diarrhea	Salivation	Edema	Convulsions, Hours
36	118	292.5	244.5	17.1	0.270	115	0	0	0	115
46	104	236.0	210.0	10.2	.....	69	0	0	0	102
47	130	309.0	238.0	15.7	.....	97	0	0	0	?
48	82	175.0	98.0	9.2 at 48 hours	.....	48	0	0	0	72
49	58	.....	.....	....	.....	45	0	0	0	24
38	102	.....	.....	....	.....	0	0	0	0	102
39	97	.....	.....	....	.....	0	0	0	0	0
Average	98.7	253.1	197.6	13.0	0.27	74	0	0	0	5

Groups V and VI (tables 8 and 9).—There were two animals in each group. They received intravenously from 100 to 500 cc. of bicarbonate Ringer's or Ringer's solution intravenously at a single injection every day after operation. The average duration of life for those receiving bicarbonate Ringer's was ninety-four hours, and for those receiving Ringer's solution the average duration of life after operation was sixty-five hours. Dog 53 in group V showed a small amount of fluid in the pleural and peritoneal cavities at autopsy; none of the other animals developed edema or ascites. More animals were not used

because of the deleterious action of the procedure. (The solution was injected slowly, 20 cc. per minute.)

Groups VII and VIII (tables 10, 11 and 12).—Group VII includes nine animals which received Ringer's solution subcutaneously (from 1,000 to 1,500 cc. daily in either two or three injections) with an average postoperative life of 165 hours, which is an average of sixty hours longer than the control animals. One of the animals (dog 57) lived 224 hours, which is 119 hours longer than the average life of a

TABLE 7.—*Data on Dogs in Group IV Following Nephrectomy*

Dog	Duration of Life, Hours	Vomiting, Hours	Diarrhea	Edema	Convulsions
40	92	48	Instituted before operation	0	0
41	88	42	Instituted before operation	0	0
42	130	48	Instituted before operation	0	0
43	60	18	Instituted before operation	0	0
44	88	48	Instituted before operation	0	0
45	89	73	Instituted before operation	0	0
	89	46	Instituted before operation	0	0

TABLE 8.—*Data on Dogs in Group V Following Nephrectomy*

Dog	Duration of Life, Hours	Vomiting	Diarrhea	Edema	Ascites	Convulsion	Bicarbonate Ringer's Injected Daily, Cc.
50	84	0	0	0	0	0	500
53	104	48	0	0	0	96	100
Average.....	94						

TABLE 9.—*Data on Dogs in Group VI Following Nephrectomy*

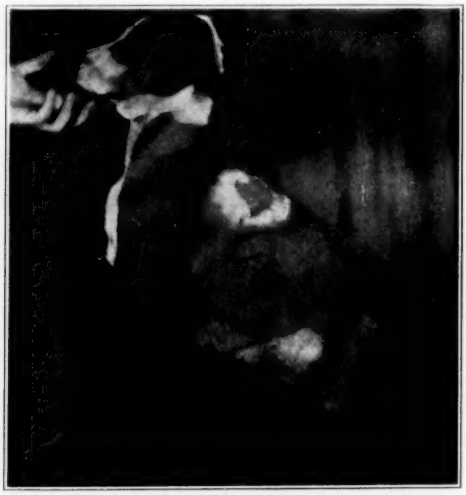
Dog	Duration of Life, Hours	Vomiting	Diarrhea	Edema	Ascites	Convulsions	Ringer's Solution Injected Daily, Cc.	
51	69	48	0	0	0	0	500	
54	62	0	0	0	0	0	500	Pulmonary edema; jaundice
Average....	65							

control animal and eighty-four hours longer than the best control animal. Two of these animals showed salivation, six of the nine had edema demonstrably before death, and six of them had collections of fluid in the pleural and peritoneal cavities demonstrable at autopsy. In dogs 57 and 61, ascitic fluid was removed by paracentesis twenty-four hours before death. At autopsy a marked cerebral and pulmonary edema was demonstrated in nearly every case. The analysis of the blood in this group demonstrated that instead of the usual drop in chlorides, there was a slight rise.

Group VIII.—This group includes five animals which received bicarbonate Ringer's subcutaneously (from 1,000 to 1,500 cc. daily in two or three injections) with an average postoperative life of 162 hours. Three of the five developed edema and four of them developed ascites.

Group IX (table 13).—There were five animals in this group, and they were given a preoperative diet of lactose, bread and milk until diarrhea developed. After operation they were given Ringer's solution subcutaneously, two to three times a day.

The average postoperative life of this group was 140 hours. Dog 18 lived 198 hours, which is ninety-three hours longer than the average



Dog 57 which lived two hundred and twenty-four hours following double nephrectomy. This dog received 1,000 cc. of Ringer's solution subcutaneously daily. Note the edema of the face, neck, limbs, body and the abdominal distention. Ascitic fluid was removed from this animal several times.

for control animals. Two of these animals salivated. The entire group developed edema and ascites.

COMMENT

There are several probable explanations which will account for the longer average postoperative life of the control animals than that observed by previous investigators. In the first place, the animals used in these experiments were all in the best physical condition and of an average weight of 18 Kg. When care is not employed in the selection of the animals and small animals in poor condition are used, the duration of life following total nephrectomy is much shorter. In the second place, the operative procedure used in these experiments was simple and rapid, thus reducing the postoperative shock to a minimum.

Lactose.—The animals that were kept on a diet of lactose, bread and milk lived thirty-two hours longer than the control animals following double nephrectomy, and the nonprotein nitrogen, urea nitrogen and creatinine accumulated more slowly in these animals on a lactose diet.

This can be explained by the fact that these animals were on a low protein diet, that the nitrogenous constituents of the blood were lower

TABLE 10.—*Typical Blood Changes in Dog 1, Group VII, Following Nephrectomy*

Date	Hours After Operation	Weight, Kg.	Nonprotein Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Gm. per 100 Cc.	Ringer's Solution Injected Daily, Cc.	Comment
7/11/28	..	22.5	34.2	1.47	.....	.....	Operation at 6 p. m.
7/12/28	24	22.6	83.9	4.2	.....	1,500	Condition good
7/13/28	48	23.6	230.5	8.0	0.447	1,500	Vomited, slight edema and salivation
7/14/28	72	24.0	300.0	8.7	0.468	1,500	Diarrhea, edema fore legs
7/15/28	96	25.6	343.8	9.2	0.484	1,500	Edema spreading
7/16/28	120	24.2	261.0	11.4	0.478	1,500	Edema of serotum
7/17/28	144	24.0	212.0	12.6	0.486	1,500	Still vomiting
7/18/28	168	24.0	344.8	13.0	0.476	1,500	Vomiting severe, edema neck
7/19/28	192	20.9	405.4	15.8	.....	1,500	Apathy, vomiting, edema less
7/20/28	199	....	.....	....	.....	.....	Died in coma during night

TABLE 11.—*Data on Dogs in Group VII Following Nephrectomy*

Dog	Duration of Life, Hours	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Chlorides as NaCl, Gm. per 100 Cc.	Vomiting, Hrs.	Diarrhea, Hrs.	Edema, Hrs.	Ascites, Hrs.	Convulsions, Hrs.	Ringer's Solution Injected Daily, Cc.	
52	201	.....	.....	....	.....	123	123	0	0	0	1,000	Pulmonary edema
56	165	.....	.....	....	.....	70	95	0	P.M.	0	1,000	Pulmonary edema
57	224	.....	.....	....	.....	115	92	142	190	0	1,000	Pulmonary edema
60	109	.....	.....	....	.....	49	49	0	0	0	1,500	Pulmonary edema
61	191	.....	.....	....	.....	68	62	68	168	0	1,500	Pulmonary edema, snuffles
1	199	405.4	.....	15.8	0.471	46	72	48	P.M.	0	1,500	Pulmonary edema
2	95	218.9	.....	13.9	0.448	0	0	72	0	94	1,500	Pulmonary edema
4	136	254.2	217.9	9.2	0.520	48	72	72	P.M.	0	1,500	Pulmonary edema
7	161	281.7	.....	11.5	0.511	72	120	120	P.M.	0	1,500	Pulmonary edema, snuffles

to start with, that the aciduric condition of the gastro-intestinal tract may decrease the absorption of toxic substances, and that the diarrhea may possibly have increased the vicarious elimination.

Histamine.—The animals that were given injections of histamine lived approximately the same time as the controls. The histamine led to a slight temporary decrease or delayed the increase of the nitrogenous constituents in the blood, which was immaterial.

The most striking observation in this group was that five of the seven dogs had convulsions. Histamine, when injected in the same amount, does not cause convulsions in normal dogs. We are at a loss for an explanation as to why it caused convulsions in these dogs.

Magnesium Sulphate.—Magnesium sulphate was used to determine the effect of diarrhea per se. It was shown that these dogs do not live

TABLE 12.—*Data on Dogs in Group VIII Following Nephrectomy*

Dog	Duration of Life, Hours	Vomiting, Hours	Diarrhea, Hours	Edema, Hours	Ascites, Hours	Convulsions	Bicarbonate Ringer's Injected Daily, Cc.	
55	133	71	96	0	P.M.	0	1,000	Pulmonary edema
58	180	118	118	0	165	0	1,500	Pulmonary edema
59	192	146	150	146	160	0	1,500	Pulmonary edema
62	121	54	99	76	P.M.	0	1,500	
63	185	72	72	72	0	0	1,500	Pulmonary edema
Average	162							

TABLE 13.—*Data on Dogs in Group IX Following Nephrectomy*

Dog	Duration of Life, Hours	Vomiting, Hours	Edema, Hours	Ascites, Hours	Convulsions	Ringer's Solution Injected Daily, Cc.	
9	142	96	120	P.M.	0	1,500	Pulmonary edema, snuffles
10	143	96	72	P.M.	0	1,000	Snuffles
11	103	94	48	P.M.	0	1,000	Snuffles
12	118	0	72	P.M.	0	1,000	Snuffles
13	198	96	144	P.M.	0	1,500	Snuffles
Average	140	..	...	.....	..		

TABLE 14.—*Summary of Data on All Groups of Dogs Following Nephrectomy*

Group	Procedure	Number of Dogs	Average Life, Hrs.	Longest Life, Hrs.	Shortest Life, Hrs.	Vomiting, Hrs.	Diarrhea, Hrs.	Numbers Having Salivation	Numbers Developing Edema	Numbers Having Convulsions
I	Control	6	105.6	140	60	74	75	1	0	0
II	Lactose diet	11	137.6	194	89	73	Before operation	0	0	0
III	Histamine	7	98.7	130	58	74	0	0	0	5
IV	Magnesium sulphate	6	89.0	130	60	46	Before operation	0	0	0
V	Bicarbonate Ringer's *	2	94.0	104	84	48	0	0	0	1
VI	Ringer's	2	65.0	69	62	48	0	0	0	0
VII	Ringer's subcutaneously	9	165.0	224	95	75	73	2	6	1
VIII	Bicarbonate Ringer's subcutaneously	5	162.0	192	121	92	107	0	3	0
IX	Lactose per os and bicarbonate Ringer's subcutaneously	5	140.0	198	103	96	Before operation	2	5	0

* Solution given intravenously.

as long as the controls, and therefore that the diarrhea, per se, has a deleterious effect on the nephrectomized dog. The diarrhea produced by the magnesium sulphate was marked and had an evident weakening effect on the dogs.

Ringer's Solution Intravenously.—The intravenous administration of Ringer's solution had such a deleterious effect on these dogs, as is shown

by the decreased length of life, that this method was discontinued, especially since an acute pulmonary edema developed in one dog.

Ringer's Solution Subcutaneously.—Our results definitely show that the subcutaneous administration of Ringer's solution prolongs the life of bilaterally nephrectomized dogs, and is the best method that we have employed. We believe that it operates by making up for the water and chlorides lost by vomiting and diarrhea and by aiding vicarious elimination. It is known that the injection of Ringer's solution increases gastric secretion, which, according to McEnery, Meyer and Ivy's work,[1] would tend to decrease nitrogenous retention. The prevention of dehydration and decrease of the sodium chloride, we believe, is the most important factor. The edema per se may prolong life by diluting the toxins in the tissues or by some unknown mechanism.

The production of edema in nephrectomized dogs is especially significant because it has long been a question as to why nephrectomized dogs do not develop edema. According to Bence,[16] nephrectomized rabbits develop edema, and it is known that rabbits do not vomit. Nephrectomized dogs begin to vomit on the second or third day, and diarrhea soon follows, which leads to dehydration and loss of chlorides. The most logical explanation for the appearance of edema in nephrectomized dogs that received Ringer's solution subcutaneously is that the tissues were supplied with water and chlorides so that edema could occur. We are not certain as to the rôle played by the chlorides in the production of the edema. But this problem is under investigation.

CONCLUSIONS

1. Control animals on a meat diet live an average of 105.6 hours following double nephrectomy, the maximum length of life being 140 hours and the minimum being sixty hours.

2. Animals on a diet of bread, milk and lactose live an average of 137.6 hours, a maximum of 194 hours and a minimum of eighty-nine hours following double nephrectomy. This is an average of thirty-two hours longer than the control animals. Therefore this diet prolongs life following double nephrectomy and delays the accumulation of nitrogenous constituents of the blood.

3. The injection of Ringer's solution subcutaneously prolongs life following double nephrectomy. The animals in this group live an average of 165 hours, which is sixty hours longer than the postoperative life of the control animals. It also produces an edema, but we are not yet prepared to state whether it is the water or the chlorides that plays the most important part in the production of this edema.

16. Bence, N.: Experimentelle Beiträge zur Entstehung der nephritischen Oedèma, Ztschr. f. klin. Med. **67**:69, 1909.

THE ACTION OF MERBAPHEN (NOVASUROL) ON THE KIDNEY OF THE DOG

A COMBINED FUNCTIONAL AND PATHOLOGIC STUDY *

HADDOW M. KEITH, M.B.
AND
B. I. JOHNSTONE, M.B.
DETROIT

Merbaphen (novasurol), an organic mercury compound, is at present being used as a diuretic in the treatment of certain patients with edema and ascites. It is well known that mercury readily damages the kidney. We [1] have shown that merbaphen, though less toxic than certain other mercurials, in sufficient doses brings about degenerative changes in the renal epithelium of the rabbit identical with that produced by the other less complex mercury compounds in common use.

In this investigation, a further study of the action of merbaphen was made by carrying out combined functional and histologic observations in the dog. Five animals were employed. As shown by MacNider [2] and Dayton,[3] the dog is subject to spontaneous renal disease. To avoid confusion from this factor, the animals were subjected to functional tests and the urine examined before merbaphen was injected. The characteristic lesions of spontaneous nephritis as described by these authors were also searched for when the kidney tissue was examined microscopically.

In a few instances the drug was given directly into the vein, but usually it was injected intramuscularly. It was diluted with physiologic solution of sodium chloride in such proportion that 0.1 cc. of merbaphen was contained in 0.5 cc. of the solution. Doses varying from 0.045 to 0.332 cc. per kilogram or from 0.2 to 0.8 cc. per animal were used. Such amounts would be equivalent to from 1 to 2.2 cc. for a man weighing 70 Kg. In one instance, a dose of 1.6 cc. was given. For varying periods before and after each injection, as indicated in the tables, the

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* From the Department of Medicine, Henry Ford Hospital, Detroit, and the Department of Pediatrics, School of Medicine and Dentistry, University of Rochester, Rochester, N. Y.

1. Johnstone, B. I., and Keith, H. M.: Toxicity of Novasurol (Merbaphen): Its Action on the Kidney of the Rabbit, Arch. Int. Med. **42**:189 (Aug.) 1928.

2. MacNider, W. de B.: A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, J. M. Research **34**:177, 1916.

3. Dayton, H.: Reliability of Dogs as Subjects for Experimental Nephritis, J. M. Research **31**:177, 1915.

urine was examined microscopically and the volume, albumin, specific gravity and total chlorides determined. The kidney function as evidenced by the phenolsulphonphthalein excretion was observed at frequent intervals. The blood chlorides and either the blood urea nitrogen or the nonprotein nitrogen were determined immediately before the injection and again twenty-four hours afterward. After the animals had been given the drug for different lengths of time, the kidneys were examined either following nephrectomy or at necropsy. Small strips of tissue were removed from different areas of each organ, preserved in 10 per cent formaldehyde, then dehydrated, fixed in paraffin, sectioned and stained with hematoxylin and eosin.

PROTOCOLS

Dog 1.—An animal weighing 13.2 Kg. was placed in a metabolism cage and given the usual scrap diet and water as desired. Observations were made on the urine and functional state of the kidneys over a preliminary period of twenty-four days. The data are summarized in table 1. There was a trace of albumin in the urine on several occasions, but the results were otherwise normal.

This animal was then given eleven doses of merbaphen over a period of five months at intervals of about two weeks, as shown in table 1. A dose of 0.2 cc. was given except in two instances, when 0.1 and 0.4 cc. were injected. The first two doses were given intravenously, the remainder intramuscularly. A dose of 0.2 cc. in this animal would be 0.015 cc. per kilogram and equivalent to approximately 1 cc. for a man weighing 70 Kg. Following the first four doses and particularly after the initial one, there was considerable diarrhea, with blood in the stools twice. This did not recur after the later doses, and the dog remained clinically well throughout the experiment. Definite diuresis resulted only following the first and tenth doses. There was no significant change in the specific gravity of the urine. Albumin occurred only occasionally and in small amounts, there being no increase over that present before the experiment was begun. No constant change was observed in the amount of chlorides excreted in the urine during the twenty-four hours following injection of the drug. The ability of the kidneys to excrete phenolsulphonphthalein was not impaired. There was no constant change in the blood chlorides as determined immediately before and twenty-four hours after merbaphen was given. The blood urea nitrogen was within the limits found by Haden and Orr[4] to be normal, except on two occasions, when it rose to 30.4 mg. per hundred cubic centimeters of blood.

Seven days after the eleventh dose, the animal was killed within four minutes by a massive dose of ether, and autopsy was immediately performed. The right kidney weighed 38 Gm. The capsule was not thickened and stripped readily, leaving a smooth, glistening, reddish surface. The cut margins did not evert. The cortex and medulla were sharply demarcated. Peripherally, the cortex was a purplish red, whereas medially fine radiating gray lines were separated by narrow reddish areas. The medulla was a dark reddish purple. The pelvis was normal. The left kidney weighed 37 Gm. and was similar in appearance to the right kidney.

In small scattered areas, however, the epithelium lining the convoluted tubules was swollen with some loss of cell boundary. The nuclei in some of the cells

4. Haden, R. L., and Orr, T. G.: Chemical Changes in the Blood of the Dog After Intestinal Obstruction, J. Exper. Med. **37**:365, 1923.

TABLE 1.—*The Effect of Merbaphen on the Blood and Urine of Dog 1, Weighing 13.2 Kg.*

	Blood		Urine						
Date, 1926	Urea Nitrogen, Mg. per 100 Cc. (Marshall)*	Chloride on Whole Blood, Mg. per 100 Cc. (Whitehorn)**	Water Intake, Cc.	Output, Cc.	Albumin, Grade	Specific Gravity	Phenolsulphonphthalein, per Cent	Total Chloride, Gm. (Whitehorn)	Comment
2/4 to 2/28	....	...	381†	279‡	1 or —	1.032§	70	2.18 (4 determinations)	
3/ 1	....	...	...	...	..	.....	..	....	Merbaphen, 0.2 cc. intravenously
3/ 2	....	...	430	490	..	.....	..	....	Mixed with feces and blood
3/ 3	....	...	730	...	..	.....	..	....	Bloody stools
3/ 4	....	...	700	610	..	.....	..	....	
3/ 5	....	...	530	140	—	1.030	..	....	
3/ 6	....	...	300	165	—	1.035	—	0.13	
3/ 7	30.4	440	...	130	..	1.027	..	....	
3/ 8	....	490	650	...	—	1.028	..	....	Diarrheal stools
3/ 9	....	...	735	420	..	.....	..	....	
3/10	....	...	...	335	—	1.030	..	....	
3/11	20.1	520	300	...	..	.....	..	....	Merbaphen, 0.1 cc. intramuscularly
3/12	....	...	100	320	—	1.032	..	0.41	
3/13	....	...	300	165	—	.....	..	....	
3/14	....	...	...	190	—	1.023	80	0.32	
3/15	....	...	...	80	—	1.030	..	0.29	
3/16	....	...	400	400	—	1.033	..	....	
3/17	....	...	250	150	3	1.033	..	....	Mixed with feces
3/18	....	...	500	240	—	1.038	..	....	Merbaphen, 0.2 cc. intramuscularly
3/19	....	...	...	...	..	.....	..	....	Diarrheal stools
3/20	....	...	700	215	—	1.036	..	....	
3/21	....	...	800	310	—	1.026	..	....	
3/22	....	...	800	...	..	.....	..	....	Diarrheal stools
3/23	....	...	400	...	..	.....	..	....	Diarrheal stools
3/24	....	...	400	200	—	1.028	..	....	
3/25	....	...	...	...	..	.....	70	....	
4/10	21.0	340	...	125	—	1.030	..	....	Merbaphen, 0.2 cc. intramuscularly
4/11	16.3	480	500	151	—	1.038	75	1.01	
4/12	....	...	280	240	—	1.038	..	2.30	
4/13	....	...	...	27	..	.....	..	....	
4/24	30.4	490	...	175	..	1.040	..	....	Merbaphen, 0.2 cc. intramuscularly
4/25	13.5	400	...	...	..	.....	80	....	
5/ 2	....	...	...	...	..	.....	..	....	Merbaphen, 0.4 cc. intramuscularly
5/16	....	...	...	...	..	.....	..	....	Merbaphen, 0.2 cc. intramuscularly
5/17	....	...	385	280	—	1.042	80	1.59	
5/18	....	...	225	135	—	1.038	..	0.88	
5/19	....	...	...	175	1	1.040	..	1.15	
5/20	....	...	...	55	—	1.029	..	....	
5/30	16.3	500	...	...	..	....	..	....	Merbaphen, 0.2 cc. intramuscularly
5/31	14.0	420	300	224	—	1.036	85	0.38	
6/ 1	....	...	250	121	—	1.029	..	1.02	
6/ 2	....	...	110	137	—	1.039	..	0.79	
6/12	....	...	...	142	—	1.037	..	0.99	
6/13	7.9	400	660	415	—	1.028	..	5.39	Merbaphen, 0.2 cc. intramuscularly
6/14	17.3	...	...	150	—	1.035	80	1.05	
6/15	...	...	720	475	—	1.032	..	8.40	
6/16	....	...	160	350	—	1.026	..	4.09	
6/17	....	...	...	120	2	1.043	..	1.03	
6/18	....	...	250	187	1	1.046	..	1.65	
6/19	....	...	...	...	2	1.044	..	....	
6/16	....	...	140	85	3	.....	..	0.90	
6/17	....	...	220	110	3	1.051	..	0.50	
6/18	....	...	270	110	3	1.035	..	0.46	
6/19	....	...	...	...	3	1.060	..	....	
6/24	....	...	...	...	—	1.028	..	....	
6/27	13.5	500	340	240	—	1.049	..	1.75	Merbaphen, 0.4 cc. intramuscularly
6/28	18.2	510	345	100	2	1.039	90	0.45	
6/29	....	...	565	295	—	1.041	..	3.19	
6/30	....	...	260	...	2	1.046	..	....	
7/ 1	....	...	305	52	2	1.014	..	0.32	
7/ 2	....	...	475	230	1	1.033	..	2.14	
7/10	....	...	390	150	1	1.035	..	0.64	
7/11	11.2	490	325	130	—	1.053	..	0.52	Merbaphen, 0.4 cc. intramuscularly
7/12	10.7	510	260	175	—	1.044	80	0.76	
7/13	....	...	375	290	—	1.042	..	4.10	
7/14	....	...	170	105	2	1.042	..	1.53	
7/15	....	...	...	225	—	1.042	..	....	
7/16	....	...	310	100	—	1.052	..	0.89	

* Van Slyke, D. D., and Cullen, G. E.: Modification of Marshall's Method, J. Biol. Chem. **19**: 211, 1914.

** Whitehorn: J. Biol. Chem. **45**: 449, 1921.

† Control average of eighteen determinations—24 hour periods; minimum, 75 cc.; maximum, 550 cc.

‡ Control average of fourteen determinations—24 hour periods; minimum, 73 cc.; maximum, 575 cc.

§ Control average of nine determinations—24 hour specimens; minimum, 1.036; maximum, 1.048.

had disappeared. There was a small amount of exudate in the lumina of a number of the convoluted tubules. The malpighian bodies were normal. There was no evidence of edema, no increase in connective tissue and no infiltration with small round cells. A few small retention cysts were scattered throughout the cortex.

Summary.—Dog 1 did not have abnormal functional or histologic manifestations to classify it as nephropathic, although there were traces of albumin in the urine on the preliminary examination. This animal was given eleven doses of merbaphen, each equivalent to approximately 1 cc. for a man weighing 70 Kg. over a period of five months. Diarrhea was present after the first four doses, but there was no further clinical evidence of toxicity. There was no constant diuresis, no decrease in the specific gravity, no increase in the albumin in the urine, and no constant increased output of chlorides. There was no diminution in the amount of phenolsulphonphthalein excreted at the end of two hours, and no constant change in the blood urea nitrogen or blood chlorides. The kidneys when examined seven days after the eleventh dose of the drug showed no gross change. Microscopically, there was evidence of a small amount of acute degeneration.

Dog 2.—An animal weighing 14.8 Kg. was studied in a similar manner, except that larger doses of merbaphen were given. Observation prior to injection of the drug revealed no abnormality. The clinical observations were similar to those in dog 1.

Twelve injections of merbaphen were given over a period of about five months at intervals of two weeks. A dose of 0.4 cc. was given except in three instances when on two occasions 0.2 cc. was injected and once, 0.8 cc. The first dose was given intravenously, the remainder intramuscularly. A dose of 0.4 cc. in this animal would be 0.024 cc. per kilogram and equivalent to 1.7 cc. for a man weighing 70 Kg. Bloody diarrhea was observed following the first dose and simple diarrhea after the early injections. The animal otherwise remained clinically well. Definite diuresis was observed only following the second and seventh doses. There was no significant change in the specific gravity of the urine. Albumin did not appear until following the last four doses, when the urine contained a moderate amount. The chloride excretion was determined following seven injections. In only two instances was there a definite increase, and this occurred during the second twenty-four hours. The phthalein excretion, which had been 80 per cent at the end of two hours before the experiment was begun, was repeatedly determined. It varied between 60 and 90 per cent, the last two determinations being 90 and 80 per cent, respectively. The test was usually carried out during the twenty-four hours following the injection of the drug, but a number of observations were made at other times to note any variation. There was no constant change in the blood urea nitrogen or blood chlorides. The former reached a level of 27.9 on one occasion, six days after the initial dose of merbaphen.

Nine days after the twelfth dose of the drug, the animal was killed within four minutes by a massive dose of ether, and autopsy was immediately performed. The kidneys each weighed 40 Gm. and were similar in appearance. The capsule was not thickened and stripped readily, leaving a smooth, glistening, dark red surface. The cortex and the medulla were sharply demarcated. The cut margins did not evert. The cortex was dark red peripherally but medially contained light lines separated by narrow reddish areas. The pyramids were dark purplish red. The pelvis and arteries were normal.

When examined histologically, a portion of the convoluted tubules, especially those in close proximity to malpighian bodies, showed a mild degree of degenera-

tion. There was some swelling of the epithelium and loss of cell boundary. The nuclei were for the most part intact. There was considerable flattening of the epithelium in some of the tubules. The lumina contained considerable homogeneous pinkish-staining exudate. Similar exudate was present in the capsular spaces of a few of the malpighian bodies. The remainder were normal. There was no evidence of edema. An occasional small area showing dense infiltration with round cells and increase in connective tissue with disappearance of the tubules was found. In these areas, the malpighian bodies had thickened capsules and partially fibrosed glomeruli. Such areas were small and were found only after careful search. The blood vessels were normal. There were a few small, cystlike spaces.

Summary.—Although a few small areas of chronic change were found histologically, since there was no albumin in the urine and functional tests were normal, dog 2 could scarcely be classified as nephropathic. This animal was given twelve injections of merbaphen, each being equivalent to 1.7 cc. for a man weighing 70 Kg., over a period of five months at intervals of two weeks. There was some diarrhea and melena following the initial doses, but except for this the dog remained clinically well. Following the last four doses, albumin appeared in the urine. The phthalein excretion and the specific gravity of the urine remained normal. No constant change was observed in the blood urea nitrogen and chlorides or urine chlorides, and diuresis was not constant. At necropsy, nine days after the twelfth dose, a small amount of parenchymal damage and a small amount of chronic change were present.

Dog 3.—An animal weighing 27.3 Kg. was studied in a similar manner. Still larger doses were given. The preliminary phthalein excretion at the end of two hours was 80 per cent, and the urine was normal.

Five doses of 0.8 cc. were given over a period of three months at intervals of two weeks. This dose would be 0.029 cc. per kilogram and equivalent to 2.05 cc. for a man weighing 70 Kg. All injections were made intramuscularly. Following the first dose there was considerable diarrhea, malaise, frothing at the mouth and grinding of the teeth. This disappeared in a few days and did not recur following subsequent doses. There was some diuresis after each dose. This was greatest following the second and third doses and was accompanied by a greatly increased intake. There was no significant change in the specific gravity of the urine. Albumin was present in the urine after each dose, being found from the second to the fourth days following injection of the drug. The phthalein excretion remained high, and the blood urea nitrogen was not increased. There was an increase in the urine chloride on three occasions, but on two of these it was delayed twenty-four hours. There was no constant change in the blood chlorides.

Seven days after the fifth dose, nephrectomy of the left kidney was done with the dog under ether anesthesia. (This animal was subsequently used for other purposes.) The left kidney weighed 60 Gm. The capsule stripped with slight difficulty, some of the tissue being torn from the otherwise smooth reddish surface. The cut margins everted slightly. The cortex and medulla were fairly sharply demarcated. The inner half of the former showed definite yellowish lines radiating outward and separated by narrow reddish areas continuous with the outer reddish portion. The medulla was a purplish color. The vessels and pelvis were normal.

On histologic examination, certain areas of proximal convoluted tubules took the acid stain more deeply than the remainder of the tissue. Here the epithelial cells were swollen, the cell boundary indistinct and the nucleus was occasionally absent. There was considerable exudate in the lumina. There was no evidence

of edema and no increase in connective tissue or infiltration with wandering cells. The malpighian bodies and blood vessels were normal. An occasional small cyst was present.

Summary.—Dog 3, a normal animal, was given five doses of merbaphen, each equivalent to 2.05 cc. for a man weighing 70 Kg., over a period of three months. She showed diarrhea and malaise after the first dose but soon recovered and remained clinically well. Diuresis occurred after each dose, and albumin appeared in the urine after the last four. The blood urea nitrogen, phthalein excretion and specific gravity of the urine remained normal. An increased output of chlorides in the urine took place on three occasions. There was no constant change in the blood chlorides. The left kidney, removed at operation seven days after the fifth dose of merbaphen, showed evidence of some acute degeneration.

Dog 6.—An animal weighing 19 Kg. was given four doses of 0.6 cc. of merbaphen over a period of one and a half months at intervals of two weeks. This dose would be 0.032 cc. per kilogram and equivalent to 2.21 cc. for a man weighing 70 Kg. The first dose caused diarrhea and considerable malaise. This soon disappeared and did not recur. A definite diuresis occurred after the first dose, but there was no definite increased output after subsequent doses. The specific gravity showed no significant change. There was no albumin following the first dose, but it was present in considerable quantities following later doses. The phthalein excretion remained high, and the blood urea nitrogen was not increased. There was an increase in the urine chlorides on two occasions. There was no constant change in the blood chlorides.

Four days after the fourth dose, nephrectomy of the left kidney was performed with the animal under ether anesthesia. The animal died twelve hours later from hemorrhage into the peritoneal cavity. Autopsy was done four hours later and the right kidney removed and examined.

The left kidney weighed 48 Gm. The capsule was slightly thickened but stripped fairly readily, the surface being torn in only a few places. The surface was otherwise smooth and was a reddish yellow. On cut section, the margins everted slightly. The cortex was sharply demarcated from the purplish medulla. The peripheral portion of the cortex was reddish brown, while the deep portion consisted of yellowish radiating lines separated by narrow reddish areas. The blood vessels and pelvis were normal.

On histologic examination the convoluted tubules showed evidence of degeneration, more widespread and involving a greater proportion of the parenchyma than in dogs 1, 2 and 3. Although there was little evidence of necrosis, the degeneration was more advanced. In addition to the swelling and loss of cell boundary, many of the nuclei were pyknotic and in a great many cells had disappeared. There was considerable exudate in the lumina. The majority of the malpighian bodies were normal. In a few there was a small amount of exudate in the capsular space. There were a few wedgeshaped subcapsular areas showing infiltration with round cells and increased connective tissue. In these, Bowman's capsule and the glomeruli had undergone some fibrosis. There were a few cyst-like spaces. The blood vessels were not abnormal.

The right kidney which was removed at autopsy showed extensive parenchymatous degeneration. About three fourths of the convoluted tubules and about one half of the ascending limbs of Henle had undergone complete necrosis. There was also swelling and vacuolization in the collecting tubules. Few normal convoluted tubules remained. Those not already completely necrosed were in the various stages of degeneration. The tubules were widely separated. Except for a small amount of exudate and fibrosis, as seen in the left kidney, the malpighian

bodies were not abnormal. A few wedge-shaped subcapsular areas of increased connective tissue and round cell infiltration were present in this kidney, as in the left. The blood vessels were not abnormal.

This dog, although apparently normal clinically, must be considered at least mildly nephropathic as evidenced by histologic examination of the kidneys after nephrectomy and at necropsy. She was given four doses of 0.6 cc. of merbaphen

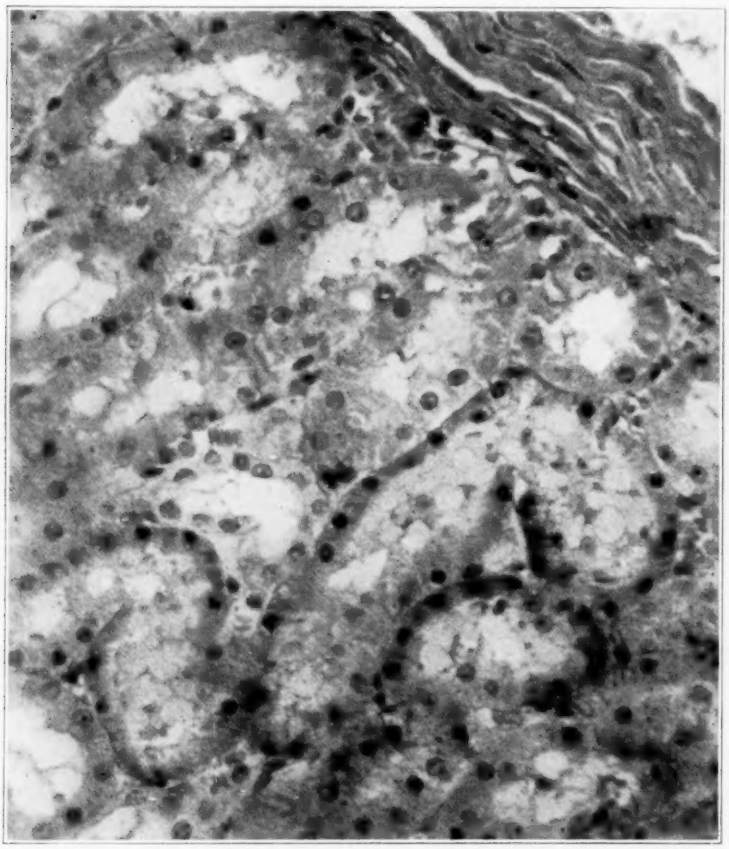

Fig. 1.—Section from the left kidney of dog 6 removed at operation four days after the fourth dose of 0.032 cc. per kilogram of merbaphen given intramuscularly. In the center of the photograph, the convoluted tubules show characteristic degeneration. The cytoplasm has partially disintegrated and that remaining has taken the acid stain more deeply than the surrounding normal tissue. The nuclei are pyknotic and the lumina are almost completely filled with débris; 16 mm. obj.

over a period of one and one-half months. Such a dose would be equivalent to 2.2 cc. for a man weighing 70 Kg. Diarrhea occurred after the first dose, and considerable albumin appeared in the urine after the last three doses. No diuresis was observed, and there was no constant increase in the total chlorides in the urine during the twenty-four hours following the injection of the drug. There was no constant change in the blood chlorides. The blood urea nitrogen, phthalein excretion and specific gravity of the urine remained unchanged. The left kidney removed at operation four days after the fourth dose showed a definite amount of early parenchymatous degeneration. The right kidney removed at autopsy sixteen hours later showed extensive tubular change. There was a small amount of chronic renal change.

Dog 7.—An animal weighing 13.2 Kg. was placed in a metabolism cage and given 320 Gm. of dog biscuit daily with water as desired. For a preliminary period of five days, the water intake and urine output were carefully determined every twelve hours. Urinalysis was carried out on each specimen and the total chlorides estimated. The blood on three occasions was examined for nonprotein nitrogen and chlorides. These preliminary results are recorded in table 2. The average intake for twelve hours was 154 cc. and the urine output, 156 cc. The average total chloride in the twelve hour urine was 0.78 Gm. A trace of albumin was found in all specimens and an occasional cast on one examination.

The animal was now given 0.3 cc. of merbaphen intramuscularly on three occasions at intervals of two and three weeks, respectively. This dose would be 0.023 cc. per kilogram and equivalent to 1.9 cc. for a man weighing 70 Kg. Before and after each injection detailed observations, summarized in table 2, were carried out every twelve hours as in the preliminary study. There was a definite diuresis on each occasion. The specific gravity showed no significant change. The albumin persisted in the urine but was not increased in amount. After the second dose a trace of reducing substance appeared in the urine. There was a slight increase in the total chlorides after one injection, but there was no constant change in the blood chlorides or nonprotein nitrogen.

One week after the third injection, a further investigation was carried out on the same animal. The twenty-four hour period was divided into three periods of eight hours each and the drug given at the beginning of the second period in the manner described by Keith and Whelan.[5] No food or water was given for the twenty-four hours. The dog was catheterized at the beginning of the experiment and at the end of each eight hours. The dose given was 0.3 cc. or 0.023 cc. per kilogram. Three similar separate investigations were carried out, as outlined in table 3. After each dose of merbaphen, definite diuresis occurred accompanied by an increase in the output of total chlorides. No increase in the albuminuria and no showers of casts were noted. The reducing substance persisted in the urine and increased slightly in amount.

The dog was now allowed to rest for four months, at the end of which time nephrectomy of the left kidney was done under ether anesthesia and the kidney examined. Microscopically there was no evidence of acute degeneration, but in some of the tubules the epithelium was a little flatter than normal. The glomeruli and blood vessels were normal. There were occasional small nests of lymphocytic infiltration and an occasional small cyst.

The animal was again allowed to rest, this time for a period of six weeks. During the next five and one-half weeks she was given frequent doses of mer-

5. Keith, N. M., and Whelan, Mary: A Study of the Action of Ammonium Chloride and Organic Mercury Compounds, J. Clin. Investigation **3**:149, 1926.

TABLE 2.—*The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 13.2 Kg.*

	Blood		Urine, 12 Hour Specimens									
Date, 1926–1927	Nonprotein Nitrogen, Mg. per 100 Cc.* (Folin and Wu)	Plasma Chloride, Mg. per 100 Cc. (Van Slyke)†	Time	Water Intake, Cc.	Output, Cc.	Specific Gravity	Albumin, Grade	Sugar, Gm.	Blood	Total (Van Slyke)† Chloride, Gm.	Microscopic Examination	Comment
12/15	35.4	595	9 p.m.	115	130	1.020	Trace	0	0	0.60	Negative	Diet, 320 Gm. of dog biscuit daily
12/16	....	...	9 a.m.	...	190	1.021	Trace	0	0	0.93	Negative	
			9 p.m.	130	145	1.025	Trace	0	0	0.59	Negative	
12/17	36.6	643	9 a.m.	140	215	1.020	Trace	0	0	1.00	Negative	
			9 p.m.	...	145	1.020	Trace	0	0	0.93	Negative	
12/18	41.4	582	9 a.m.	201	165	1.023	Trace	0	0	0.69	Negative	
			9 p.m.	150	130	1.027	Trace	0	0	0.68	Three granular casts, white blood cells	
12/19	....	...	9 a.m.	140	Lost							
			9 p.m.	250	140	1.028	Trace	0	0	0.54	Few white blood cells	
12/20	....	...	9 a.m.	90	145	1.024	Trace	0	0	0.79	Oxalates and urates	
			9 p.m.	185	140	1.017	Trace	0	0	0.26	Negative	Merbaphen, 0.3 cc. intramuscularly
12/21	36.2	559	9 a.m.	100	390	1.016	Trace	0	0	0.62	Negative	
			9 p.m.	90	85	1.026	Trace	0	0	0.36	Few white blood cells	
12/22	38.6	482	9 a.m.	250	125	1.030	Trace	0	0	0.68	Few white blood cells	
			9 p.m.	125	186	1.030	Trace	0	0	0.52	Negative	
12/31	40.6	606	9 a.m.									
1/ 1	....	...	9 p.m.	250	155	1.028	Trace	Trace	0	1.15	Negative	
1/ 2	....	...	9 a.m.	65	187	1.038	Trace	Trace	0	0.61	Negative	
			9 p.m.	...	165	1.038	.....	Trace	0	0.64	Few pus cells	Merbaphen, 0.3 cc. intramuscularly
1/ 3	37.5	577	9 a.m.	200	320	1.015	1	0	0	1.77	Negative	
			9 p.m.	100	233	1.010	1	0	0	0.31	Negative	
1/ 4	....	...	9 a.m.	230	257	1.025	Trace	0	0	0.37	Negative	
			9 p.m.	180	96	1.025	Trace	0	0	0.21	Negative	
1/ 5	....	...	9 a.m.	115	236	1.023	Trace	Trace	0	1.77	Negative	
1/17	34.8	630	.....	...	...	.....	.....	...	...	....	.....	Phenolsulphonphthalein, 65 per cent
1/22	....	...	9 p.m.	160	115	1.039	Trace	1+	0	1.04	Many pus cells	
1/23	....	...	9 a.m.	50	118	1.030	1	Trace	?	0.95	Many red blood cells; 2 casts; white blood cells	
			9 p.m.	80	185	1.031	?	?	0	1.65	Few white blood cells	Merbaphen, 0.3 cc. intramuscularly
1/24	37.2	555	9 a.m.	...	356	1.029	?	0	?	1.79	Red and white blood cells; epithelial cells	
			9 p.m.	200	106	1.023	?	?	0	0.46	Many pus cells	
1/25	47.2	615	9 a.m.	140	110	1.034	?	Trace	0	0.33	Red blood cells; white blood cells; epithelial cells	Phenolsulphonphthalein, 54 per cent
			9 p.m.	215	130	1.029	Trace	?	0	0.12	Red blood cells; white blood cells	
1/26	....	...	9 a.m.	60	112	1.026	?	Trace	0	0.75	Few red blood cells and white blood cells	
			9 p.m.	93	118	1.027	Trace	?	0	0.61	Few red blood cells and white blood cells	

* Folin and Wu: J. Biol. Chem. **38**: 81, 1919
† Van Slyke: J. Biol. Chem. **58**: 523, 1923-1924.

baphen, at first every three to five days, and later every other day. In all, fourteen doses of 0.3 cc. or 0.023 cc. per kilogram were given and observations carried out as outlined in table 4. During the first three weeks diuresis occurred after each injection, except the second. Later this was not so pronounced, although the average daily output was increased from approximately 260 to 408 cc. Albumin persisted, with little change in the amount. The reducing substance remained constantly in the urine in measurable amounts. After the fourth injection casts appeared, and following later doses, they gradually increased in number. Following nine of the fourteen injections, the total chlorides were increased; after two, the specimens were lost; and after three, they were the same or decreased. The blood nonprotein nitrogen was somewhat above normal on three occasions and within normal limits on three. The elevation was not marked and was possibly due to the fact that the remaining kidney was slightly overtaxed by repeated doses of the drug. Three months after the completion of the experiment the nonprotein nitrogen was normal on two occasions, demonstrating the absence of

TABLE 3.—*The Effect of Merbaphen on the Urine of Dog 7, Weighing 13.2 Kg.**

		Urine						
Date, 1927	Time	Output, Cc.	Specific Gravity	Albumin, Grade	Reducing Substance	Chloride, Gm. (Van Slyke)†	Microscopic Examination	Comment
1/30	11 p.m.	..	.....	..	..	....	.....	Catheterized
1/31	7 a.m.	51	1.048	Trace	1	0.40	Many pus cells.....	Merbaphen, 0.3 cc. intramuscularly
	3 p.m.	75	1.039	Trace	Trace	1.30	Pus cells and erythrocytes	
	11 p.m.	41	1.042	1	Trace	0.43	Pus cells and erythrocytes	
2/16	11 p.m.	..	.....	..	..	....	.....	Catheterized
2/17	7 a.m.	57	1.051	..	2	0.49	Few erythrocytes.....	Merbaphen, 0.3 cc. intramuscularly
	3 p.m.	92	1.033	Trace	3	0.70	Many erythrocytes	
	11 p.m.	42	1.036	Trace	Trace	0.27	Many erythrocytes; some leukocytes	
3/ 9	11 p.m.	..	.....	..	..	....	.....	Catheterized
	7 a.m.	60	1.055	..	3	0.83	Erythrocytes; leukocytes	Merbaphen, 0.3 cc. intramuscularly
	3 p.m.	74	1.040	Trace	2	1.37	Erythrocytes; leukocytes	
		44	1.040	Trace	2	0.15	Erythrocytes; leukocytes	

* During these experiments the dog received no food or water. All specimens of urine were obtained by catheter.

† Van Slyke: J. Biol. Chem. **58**: 523, 1923-1924.

permanent renal injury. During the final two weeks of the experiment, the dog refused some of her diet and was much less active than usual. There was no vomiting.

For the next five months, she was given a general hospital scrap diet, and at the end of this period weighed 17.5 Kg. and appeared well. The urine contained no albumin, sugar or casts. The dog was again placed in a metabolism cage and given no food or water for twenty-four hours. She was catheterized before the experiment was begun and at the end of each eight hours. At the end of the first eight hours, she was given a dose of 1.6 cc. of merbaphen intramuscularly. Such a dose would be 0.09 cc. per kilogram and corresponds to that which we[1] found to be the maximum single tolerated dose for a normal rabbit. This resulted in a marked diuresis with a great increase in the total urine chlorides, as shown in table 5. During the third eight hours, there were showers of finely granular and cell casts in the urine. No reducing substance was noted. About thirty-six hours after the drug was given the animal vomited, became drowsy and weak, and passed numerous soft and liquid stools. The vomiting and malaise increased, and after five days the dog died. Autopsy was performed immediately.

TABLE 4.—*The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 14.1 Kg.*

	Blood		Urine							
Date, 1927	Nonprotein Nitrogen, Mg. per 100 Cc. (Folin and Wu)*	Plasma Chloride, Mg. per 100 Cc. (Van Slyke)†	Water Intake, Cc.	Output, Cc.	Specific Gravity	Albumin, Grade	Reducing Substance, Gm.	Total (Van Slyke) Chloride, Gm.	Microscopic Examination	Comment
7/ 6	....	...	...	...	.....	.....	....	....	.....	Merbaphen, 0.3 cc. intramuscularly
7/ 7	....	...	110	425	1.025	Trace	1	4.14	Red and white blood cells	
7/ 8	56.1	581	160	128	1.057	Trace	2	0.99	Red and white blood cells.....	Diet, 320 Gm. dog biscuit daily
7/ 9	....	...	140	126	1.049	—	0.45	1.36	Red and white blood cells	
7/10	....	...	140	173	1.043	—	1	2.35	Red and white blood cells	
7/11	....	...	260	329	1.028	—	1	2.61	Red and white blood cells.....	Merbaphen, 0.3 cc. intramuscularly
7/12	....	...	...	310	1.028	2	1	2.17	Red blood cells and epithelial cells	
7/13	....	...	210	142	1.044	Trace	0.36	1.35	Red and white blood cells	
7/14	....	...	115	145	1.050	Trace	1	1.76	Red blood cells	
7/15	....	...	235	158	1.052	—	0.46	1.91	Red blood cells.....	Merbaphen, 0.3 cc. intramuscularly
7/16	....	...	65	420	1.026	Trace	0.06	3.94	Red blood cells and granular casts	
7/17	....	...	240	130	1.049	—	1	0.78	Red and white blood cells	
7/18	....	...	?	272	1.034	—	1	1.90	Red and white blood cells	
7/19	....	...	?	238	1.040	1	1	1.78	Red and white blood cells.....	Merbaphen, 0.3 cc. intramuscularly
7/20	....	...	70	350	1.031	—	?	3.33	Granular and tubular casts	
7/21	64.6	581	90	173	1.049	—	1	1.28	Granular casts and red blood cells	Merbaphen, 0.3 cc. intramuscularly
7/22	....	...	30	370	1.030	—	1	3.15	Pus cells	
7/23	....	...	410	166	1.041	Trace	1	0.99	Many granular casts.....	Merbaphen, 0.3 cc. intramuscularly
7/24	....	...	115	347	1.039	Trace	0.96	2.81	Granular and cell casts	
7/25	....	...	80	420	1.030	Trace	1	2.55	Few granular casts; pus.....	Merbaphen, 0.3 cc. intramuscularly
7/26	29.0	...	...	365	1.033	Trace	0.64	1.35	Few granular casts; pus	
7/27	....	...	385	350	1.038	1	2	0.71	Many granular casts.....	Merbaphen, 0.3 cc. intramuscularly
7/28	....	...	295	Lost					Granular casts; pus.....	Merbaphen, 0.3 cc. intramuscularly; phenolsulphonphthalein, 44.3 %
7/29	32.6	...	280	330	1.033	2	2.75	0.91		
7/30	....	...	435	425	1.024	1	1.77	1.42	Many granular casts	
7/31	....	...	210	420	1.032	1	2.14	1.75	Granular and waxy casts	
8/ 1	....	...	410	350	1.020	1	1	0.88	Many granular casts.....	Merbaphen, 0.3 cc. intramuscularly
8/ 2	....	...	...	330	1.025	Trace	1.61	1.62	Many granular casts	
8/ 3	....	...	400	338	1.020	1	0.99	0.53	Granular casts; pus.....	Merbaphen, 0.3 cc. intramuscularly
8/ 4	....	...	370	365	1.025	Trace	1	1.13	Granular casts; pus	
8/ 5	38.5	500	400	360	1.014	Trace	Trace	1.54	Granular casts; pus.....	Merbaphen, 0.3 cc. intramuscularly
8/ 6	....	...	310	355	1.015	Trace	1	0.72	Granular casts epithelial cell	
8/ 7	....	...	145	350	1.029	Trace	1	1.62	Pus cells and epithelial cells.....	Merbaphen, 0.3 cc. intramuscularly
8/ 8	....	...	?	Lost						
8/ 9	....	...	120	433	1.020	—	1	2.26	Granular casts, pus cells	
8/10	....	...	...	487	1.018	Trace	Trace	1.86	Granular casts and pus.....	Merbaphen, 0.3 cc. intramuscularly
8/11	....	...	265	615	1.015	Trace	Trace	2.42	Granular casts and pus	
3/12	....	...	550	475	1.017	1	Trace	1.87	Granular casts and pus	
8/13	55.0	616	...	540	1.017	1	Trace	1.93	Many granular casts	
11/ 1	32.0									
11/30	42.8									

* Folin and Wu: J. Biol. Chem. **38**: 81, 1919.
† Van Slyke: J. Biol. Chem. **58**: 523, 1923-1924.

The left kidney had been previously removed. The right kidney was pale and small but smooth, and the capsule stripped readily. The cut edges rolled out slightly. The cortex was uniformly pale. The medulla was a chocolate red.

On histologic examination, there was widespread parenchymatous degeneration. The majority of the convoluted tubules and ascending limbs of Henle had undergone complete necrosis. The remainder showed various stages of degeneration.

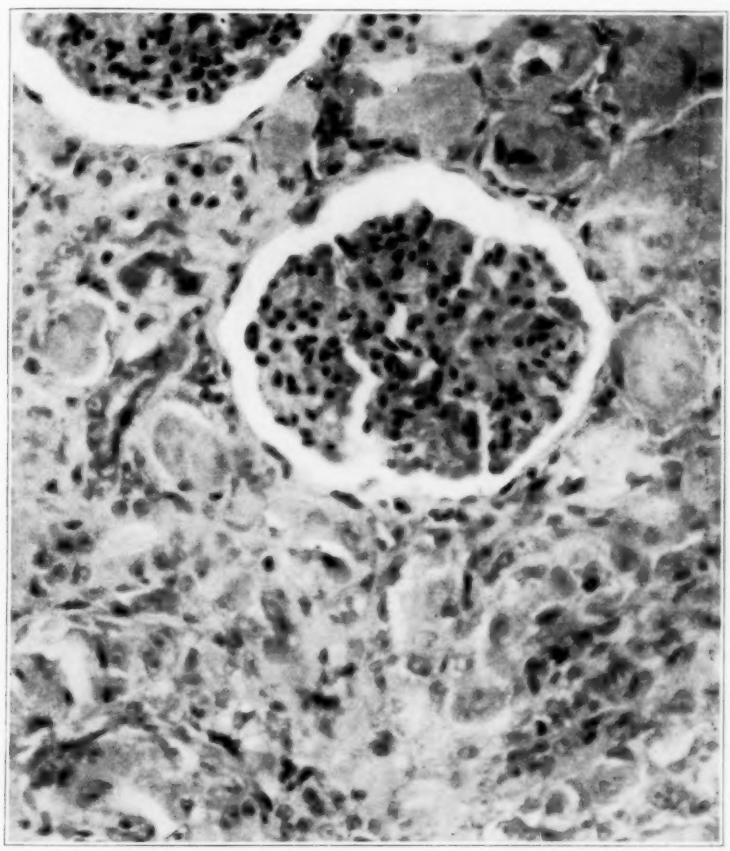

Fig. 2.—Section from the right kidney of dog 7 removed at autopsy five days after a single lethal dose of merbaphen. The glomeruli are normal. The epithelium of the convoluted tubules for the most part shows either complete necrosis or the various stages of regeneration; 16 mm. obj.

A good deal of exudate and a large number of casts were present in the lumina. The malpighian bodies were normal except that a few showed a little homogeneous exudate in the capsular space. There was some evidence of edema. Considerable regeneration was found, as evidenced by the presence of large irregular

cells with vesicular nuclei and bluish-staining cytoplasm. In some areas, the necrotic material was surrounded by irregular young cells. Some of the tubules were lined by flattened epithelium, although this was not a prominent feature. No calcium deposition was seen. As described in the left kidney, there were a few small areas of lymphocytic infiltration and a number of small cysts.

Summary.—Dog 7 was used for a number of different experiments during which the diet was carefully controlled. A trace of albumin was found in the urine before the study was begun, but nothing further was found to classify the animal as nephropathic. In the first experiment, three doses of 0.3 cc. of merbaphen were given at rather long intervals. Following each injection there was diuresis, and after one, an increased chloride output in the urine. A trace of reducing substance appeared in the urine, but no other evidence of toxicity was observed. There was no constant change in the blood chlorides.

One week after the first experiment, a second, similar to the first except that no food or water was given for twenty-four hours, was started. A dose of 0.3 cc. was given on three separate occasions, at considerable intervals. A definite

TABLE 5.—*The Effect of Merbaphen on the Blood and Urine of Dog 7, Weighing 17.5 Kg.*

		Urine						
Date, 1928	Time	Output, Cc.	Specific Gravity	Albumin, Grade	Reducing Substance	Total Chloride, Gm. (Van Slyke)*	Microscopic Examination	Comment
3/27	11 p.m.	...	.....	—	0	....	Red and white blood cells; no casts	
3/28	7 a.m.	113	1.043	2	..	0.97	Red and white blood cells; no casts	Merbaphen, 1.6 cc. intramuscularly
3/28	3 p.m.	715	1.013	1	0	6.30	Red and white blood cells; no casts	
3/28	11 p.m.	82	1.024	2	0	0.47	Shower of finely granular casts; red and white blood cells	
4/2	.....	..	.....	2	0	....	Red and white blood cells; no casts	

* Van Slyke: J. Biol. Chem. **58**: 523, 1923-1924.

diuresis and increased output of chlorides resulted following each injection. There was no evidence of toxicity except that the reducing substance increased in amount.

Four months later, the left kidney was removed under anesthesia and when examined microscopically did not show acute degeneration.

After a further rest of six weeks, fourteen doses of 0.3 cc. were given at short intervals over a period of about one and one-half months. Except following the last few doses, a definite diuresis and an increased chloride excretion occurred. Signs of toxicity appeared toward the end of this experiment in the form of general malaise and increased albumin and casts in the urine.

During the next five months, the animal was allowed to rest and at the end of that time appeared well. A single dose was now given which, although a marked diuresis and increased chloride excretion had occurred, proved lethal five days later. At autopsy, extensive tubular degeneration with considerable evidence of regeneration was found.

COMMENT

Saxl and Heilig,[6] Nonnenbruch,[7] Muhling [8] and others have shown that merbaphen produces a relative and absolute increase in the urine chlorides both in normal patients and in those with edema. Keith and Whelan [9] have confirmed these observations and have also found this to be true in the dog. Crawford and McIntosh [10] expressed the belief that the increase in chloride output persists longer than the diuresis. In this study in dogs 1, 2, 3 and 6, we did not find a constant increased chloride excretion in the urine following the injection of merbaphen. In these animals, however, the chloride intake was not controlled. In dog 7, in which a constant diet was maintained, the chloride excretion following the injection of merbaphen was always increased. Various writers have found diuresis to be inconstant in the normal subject. In our experiments an increase in urine output following the injection of merbaphen occurred only when the fluid intake was limited or when no fluid was given. Crawford and McIntosh [10] found that in human patients studied by them there was a definite lowering of the plasma chlorides at the end of four and one-half hours. Other observers have not found such constant changes. Keith and Whelan [5] reported that the changes in concentration of the blood chlorides following injection of merbaphen are variable and never marked in degree. They found no change in the carbon dioxide combining power and no significant change in the nonprotein nitrogen of the blood. In this study, no constant changes were found in the blood chlorides when examined twenty-four hours after injection of the merbaphen.

The doses used per kilogram were comparable to amounts used therapeutically in man, except in one instance. This was in dog 7, that was given 1.6 cc., which proved lethal. This was 0.09 cc. per kilogram and equivalent to 6.3 cc. for a man weighing 70 Kg. Except in one experiment, the intervals between doses were somewhat longer than those allowed as a rule when the drug was used as a diuretic. In this one exception, the interval was reduced to as short as one day over a period of about five weeks.

6. Saxl, P., and Heilig, R.: Ueber die diuretische Wirkung von Novasurol und anderen Quecksilber Injectionen, Wien. klin. Wcnschr. **33**:943, 1920.

7. Nonnenbruch, W.: Ueber die Wirkung des Novasurols auf Blut und Diurese, Munchen. med. Wchnschr. **68**:1282, 1921.

8. Muhling, A.: Studie ueber die diuretische Wirkungsweise von Quecksilber, ausgefürt mit dem organischen Quecksilberpraparat Novasurol, Munchen. med. Wchnschr. **68**:1447, 1921.

9. Keith and Whelan (footnote 5). Keith, N. M., and Whelan, Mary: The Effect of Novasurol on the Composition of Blood and Urine, Am. J. Physiol. **72**:195, 1925.

10. Crawford, J. H., and McIntosh, J.: Observations on the Use of Novasurol in Edema Due to Heart Failure, J. Clin. Investigation **1**:333, 1925.

Bloody diarrhea and malaise were observed occasionally after the initial doses, but this was not seen subsequently unless the drug was given in large amounts or at short intervals. Albumin was found after the larger doses, especially if repeated. It was definitely increased in three instances, namely, in dog 6 after the last three doses, each of which was 0.6 cc.; in dog 7 after several doses of 0.3 cc. repeated at short intervals, and again in dog 7 after the lethal dose of 1.6 cc. In the last two instances, albumin was accompanied by casts. When the animal was allowed to rest, signs of toxicity and renal irritation quickly disappeared. A reducing substance was present in the urine of dog 7 following the later doses.

As evidenced by the phthalein excretion, blood urea or nonprotein nitrogen, and the specific gravity of the urine, no chronic functional renal damage could be demonstrated even after the drug had been given over a period of five months.

Examination of the kidneys of those animals to which merbaphen had been given in repeated doses, and at intervals corresponding to what is recognized as correct therapeutically for man, showed slight parenchymatous change. Such kidneys were examined from three to nine days after the final dose of the drug. There was also found considerable exudate in the lumina. In dog 7, when the kidney was not examined for four months after the administration of merbaphen, no degenerative change was present. In dog 6 the right kidney was removed at autopsy following death due to intraperitoneal hemorrhage. The extensive degeneration found is considered to be due to the combined action of merbaphen, ether and postmortem change in an already damaged kidney.

Dog 7 died five days following a dose of 1.6 cc. This amounted to only 0.09 cc. per kilogram. We [1] found this amount to be the maximum single tolerated dose per kilogram in the normal rabbit. At this time, however, dog 7 possessed only one kidney and six weeks previously had been given repeated large doses of merbaphen. These factors doubtless explain the small amount necessary to produce death in this animal. It is interesting to note that following this lethal dose marked diuresis and an increased output of urine chlorides occurred.

The right kidney of dog 7, removed immediately after death, showed extensive tubular damage. There was almost complete necrosis of all the convoluted tubules and ascending limbs of Henle, with little change in the glomeruli. Considerable evidence of regeneration was present but no calcium deposition. The histologic picture seen in this kidney corresponds closely with that seen in the kidney of the rabbit dying from a single lethal dose of merbaphen.

The early changes described in the other kidneys are also similar to those seen in the kidney of the rabbit when small doses have been given. Lazarus-Barlow [11] observed similar early degenerative changes in rabbits killed three days after three doses of 0.2 cc. of merbaphen given at intervals of three days. MacNider [2] pointed out how readily renal epithelium, especially that which is already the seat of slight degeneration, undergoes further change early after death. The tissue used in this study was removed at operation or immediately after death and preserved at once in 10 per cent formaldehyde. It is thus improbable that autolytic change in the parenchyma brought about this slight degeneration. It is known that ether will injure the tubular epithelium of the kidney, and albumin and casts are commonly found in the urine for from one to three days following anesthesia. MacNider [12] showed that in the normal dog after morphine-ether anesthesia lasting from two and one-half to three hours the kidney parenchyma is normal histologically. In the naturally nephropathic animal, however, under similar circumstances some parenchymatous degeneration is often found, especially if the dog is first given uranium nitrate and then placed under the anesthetic.

It is possible that mercurials in conjunction with ether might have a similar effect. It is doubtful, however, whether ether given for four minutes could produce demonstrable degeneration in the kidney even when given in conjunction with merbaphen. On the other hand, when nephrectomy was done ether was used as an anesthetic over a period of about one hour. It is conceivable that in such instances degenerative changes might have been made more extensive by ether. That such a result, if present, must be slight is borne out by the entire absence of degeneration in the left kidney of dog 7 removed by nephrectomy.

It is accordingly felt that the renal degeneration present, together with the casts and exudate in the lumina, is direct evidence of the toxic effect of merbaphen on the tubular epithelium. There is little doubt that such change is readily repaired in the normal subject provided suitable rest periods are given and the doses used are not too large. No evidence was found to prove that any chronic change resulted from the continued use of the drug. The chronic changes described could not be attributed to merbaphen but were probably spontaneous. MacNider [2] considered only those dogs nephropathic which prior to autopsy showed albumin intermittently or constantly in the urine together with various types of casts and at autopsy showed unquestionable evidence of fairly diffuse renal injury. According to this standard, none of the dogs used in this study could be considered as definitely nephropathic.

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11. Lazarus-Barlow, P.: The Effect of Intravenous and Intramuscular Inoculations of Novasurol in Rabbits, Lancet **1**:127, 1928.

12. MacNider, W. deB.: A Pathological and Physiological Study of the Naturally Nephropathic Kidney of the Dog, Rendered Acutely Nephropathic by Uranium or by an Anesthetic, J. M. Research **34**:199, 1916.

SUMMARY

Five dogs were given merbaphen in amounts corresponding to doses used therapeutically in man at varying intervals for periods up to five months. When the fluid and chloride intake were carefully controlled, and a sufficient period was allowed between doses of the drug, a diuresis and an increase in the urine chlorides always occurred during the twenty-four hours following the injection of the drug. On the other hand, when they were not controlled, both diuresis and increase in chloride output were inconstant. There was no constant change in the blood chlorides. The specific gravity and phthalein excretion remained normal. Albumin appeared irregularly, particularly after large doses repeated at short intervals. Casts also appeared after toxic doses. When the kidneys were examined histologically, there was evidence of early degeneration from three to nine days after the final doses of the drug. Some chronic change was present. This could not be attributed to merbaphen and was considered spontaneous. The kidney of one dog dying five days after a single lethal dose showed widespread tubular necrosis similar to that observed in the kidney of the rabbit and to that shown by various writers to be produced by toxic doses of other mercury compounds in common use.

CONCLUSIONS

1. If the fluid intake is limited and the chloride intake is constant, diuresis with increase in the relative and total urine chloride always occurs following the injection of merbaphen. There is no constant change in the blood chlorides.

2. Repeated doses of merbaphen corresponding in amount to doses used therapeutically in man given over a period of five months produced no functional change in the kidney of the dog as evidenced by blood urea or nonprotein nitrogen, specific gravity, or phthalein excretion.

3. The kidneys of animals given repeated doses showed evidence of slight degeneration when examined histologically from three to nine days following the final dose. This was more marked following the larger doses and disappeared if the drug was discontinued.

4. In toxic doses the action of merbaphen on the renal parenchyma of the dog is similar to its action on the kidney of the rabbit and to the action of other mercury compounds in common use.

SECRETION OF BILE IN RESPONSE TO RECTAL INSTILLATIONS*

ABRAHAM LEON GARBAT, M.D.
Attending Physician, Lenox Hill Hospital
AND
HARRY GEORGE JACOBI, M.D.
Associate Attending Physician, Lenox Hill Hospital
NEW YORK

Various studies in connection with the physiology of the secretion of bile have clearly shown that bile is being secreted constantly. The passage of bile into the intestines, however, occurs at intervals; for the liver, unlike every other gland except the kidney, has in connection with it a reservoir, the gallbladder, in which the bile accumulates and from which it is only expelled periodically.

One must, therefore, clearly understand and distinguish the bile-secreting from the bile-expelling mechanism. Heretofore, investigators attempting to study these two phases of secretion and expulsion have limited themselves to the response obtained after oral administration of different foods and chemicals. With the aid of the dye method, which visualizes the gallbladder, one is able to demonstrate the rate of filling and emptying of this reservoir following the intake of various foods and drugs. It is difficult to tell, however, whether the flow of bile thus obtained is simply a result of the secretion from the liver alone or whether it is associated with the emptying of the gallbladder; naturally, both factors may play a rôle.

Of the direct influence of nerves either on the secretion of bile or its expulsion, we have little definite knowledge. It is true that the secretion of bile or its expulsion may be distinctly affected by the section and stimulation of nerves which control the blood supply to the stomach, intestines and spleen, for the quantity of blood passing through these organs and the rate of secretion are diminished when the blood supply is greatly lessened. In this way, stimulation of the medulla oblongata, the spinal cord or the splanchnic nerves stops or slows the secretion of the bile by constricting the abdominal vessels, and the same effect can be reflexly produced by the excitation of afferent nerves.

Just what effect the instillation of various solutions high up in the lower bowel would have on the secretion and expulsion of bile was a question which presented itself during investigations in connection with another problem. In every instance we noted that shortly after the intro-

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duction of different solutions high up into the rectum, a flow of bile was obtained from the duodenal tube. This occurred within fifteen minutes after the rectal instillation and lasted from thirty to forty-five minutes. The bile was always light yellow at the onset and occasionally became darker as the drainage continued. Our next object was to determine whether this flow of bile was actually initiated by the instillation of these various liquids, and if so, what was the source of the bile? Did it come from the gallbladder or from the liver? Was it a phenomenon of liver secretion or of contraction of the gallbladder or of both?

A group of patients apparently free from disease was selected for investigation. Each patient was given a cleansing high enema at night, and after that the duodenal tube was passed. The next morning the proper position of the duodenal tube was ascertained, and aspiration was attempted to determine whether there was a spontaneous flow of bile through the tube. A large size rectal tube was then introduced as high up into the bowels as possible without causing the patient too much discomfort, usually about 12 inches (30.4 cm.). One hundred fifty cubic centimeters of one of various solutions was next injected through the tube. The tube was then clamped at the end and left in place. At short intervals thereafter, aspiration of the duodenal tube was practiced, and the time of onset and cessation of the flow of bile was determined. In some cases the flow of bile started without aspiration. Chemical examinations of the blood and white blood cell counts and differential counts were made at varying intervals during the drainage of the bile.

The solutions employed for the instillations were (1) physiologic solution of sodium chloride; (2) indigo carmine (40 cc., 4 per cent); (3) dextrose (100 Gm.); (4) phenolphthalein (2 cc. standard alkaline solution to 150 cc. physiologic solution of sodium chloride); (5) methylene blue (methylethionime chloride, U.S.P.) (2 cc. 5 per cent solution to 150 cc. distilled water); (6) peptonized milk (150 cc.).

REPORT OF CASES

GROUP 1: CASE 1.—A man, aged 53, was admitted to the hospital with a diagnosis of chronic arthritis. On the evening of Feb. 12, 1928, the duodenal tube was passed, and a high cleansing enema was given. On February 13, 150 cc. of phenolphthalein solution was injected through the rectal tube at 8:50 a. m., and a flow of bile was noted at 9 a. m., which continued until 9:45 a. m. A specimen of urine collected at 10 a. m. showed the presence of phenolphthalein. The two hour urinary excretion of phenolphthalein, following the rectal injection, was 11 per cent. No kidney lesion was present. On February 15, the procedure was repeated, but this time physiologic solution of sodium chloride was introduced at 9:10 a. m. At 9:21 a. m. a flow of bile was obtained, which continued until 9:45 a. m.

CASE 2.—A man, aged 27, was admitted to the hospital with a diagnosis of malnutrition. On Feb. 18, 1928, 150 cc. of peptonized milk was instilled into the rectum at 9:12 a. m. At 9:19 a. m., a flow of bile was obtained from the duodenal tube; it was extremely profuse and continued until 10:20 a. m. On February 22,

this procedure was repeated and 150 cc. of a solution of phenolphthalein was introduced through the rectal tube at 8:55 a. m. The flow of bile commenced at 9:01 a. m. and continued until 9:35 a. m. At 10:15 a. m. a specimen of urine showed the presence of phenolphthalein. The total amount of phenolphthalein recovered in the urine at the end of two hours was 18 per cent. The subsequent functional tests of the kidney in this patient showed a normal excretion of phenolsulphonphthalein and failed to reveal any kidney insufficiency.

CASE 3.—F. B., a man, aged 46, was admitted to the hospital for observation, but no pathologic condition was discovered.

On Feb. 24, 1928, 150 cc. of physiologic solution of sodium chloride was injected through the rectal tube at 9:05 a. m. A flow of bile was obtained from the duodenal tube at 9:12 a. m., and it continued until 9:45 a. m. On February 26, this procedure was repeated, peptonized milk being used. The milk was injected through the rectal tube at 9:12 a. m., and a flow of bile was obtained at 9:17 a. m.; this continued until 9:54 a. m.

CASE 4.—E. M., a man, aged 21, who was convalescing from a lobar pneumonia, was admitted to the hospital for observation.

On March 6, 1928, 150 cc. of physiologic solution of sodium chloride was instilled into the rectum at 9:15 a. m. At 9:18 a. m., a flow of bile was obtained which was profuse and continued until 10 a. m. On March 8, at 8:45 a. m., this procedure was repeated, 150 cc. of an indigo carmine solution being used. A flow of bile started at 8:53 a. m. and continued until 9:15 a. m. On March 9, we attempted to see what effect simple inflation of the bowel with air would have on the flow of bile. At 9:05 a. m., the lower bowel was distended to a moderate degree. No bile was obtained from the duodenal tube in spite of repeated aspirations for a period of one hour.

CASE 5.—J. L., a man, aged 45, was admitted with a diagnosis of ulcer of the stomach.

On March 11, 1928, 150 cc. of physiologic solution of sodium chloride was introduced into the rectum at 8:45 a. m. At 8:48 a. m., a flow of bile began spontaneously from the duodenal tube and continued until 9:20 a. m.

CASE 6.—S. G., a man, aged 37, was admitted to the hospital with a diagnosis of gastric ulcer.

On March 12, 1928, the duodenal tube was passed at 9 p. m. On March 13, at 9 a. m., 150 cc. of peptonized milk was injected through the rectal tube. At 9:12 a. m., bile began to flow and continued to flow until 10 a. m.

The white blood cell count and differential count and the results of chemical examination of the blood in this case are recorded in the accompanying table.

CASE 7.—C. P., a man, aged 22, was admitted to the hospital for observation, but no pathologic process was discovered.

On March 26, 1928, 150 cc. of a solution of methylene blue was injected into the rectum at 9:05 a. m. At 9:17 a. m., bile started to flow from the duodenal tube and continued until 9:55 a. m. Methylene blue made its appearance in the urine at 10:30 a. m.

CASE 8.—J. F., a man, aged 67, was admitted to the hospital with a diagnosis of mild diabetes.

On April 2, 1928, 150 Gm. of dextrose was given per rectum at 9:20 a. m. At 9:27 a. m., bile began to flow from the duodenal tube and continued to do so until 10:15 a. m. The blood sugar determination made at 9:10 a. m. just before the instillation, showed 180 mg.; at 10:10 a. m., it was 192 mg.; at 12:15 p. m., 200 mg.

Thus, it is noted from this group of cases that flow of bile was stimulated by simple instillation of various fluids into the rectum.

The results obtained in all of the cases are recorded in the accompanying table.

After these experiments were completed, a second group of apparently normal persons was selected for study in order to establish whether the flow of bile came from the liver or from the gallbladder and

A Review of Eight Cases in Group 1, Showing the Effect of Rectal Injections on the Flow of Bile

Case	Date	Solution Used for Rectal Injection	Time	Time of Appearance of Bile from Duodenal Tube	Time of Cessation of Bile Flow	Remarks
1	2/13/28	150 cc. phenolphthalein	8:50 a. m.	9:00 a. m.	9:40 a. m.	At 10 a. m. phenolphthalein was detected in urine
	2/15/28	150 cc. physiologic solution of sodium chloride	9:10 a. m.	9:21 a. m.	9:45 a. m.	
2	2/18/28	150 cc. peptonized milk	9:12 a. m.	9:19 a. m.	10:20 a. m.	
	2/22/28	150 cc. phenolphthalein	8:55 a. m.	9:01 a. m.	9:35 a. m.	At 10:15 a. m. phenolphthalein was detected in urine
3	2/24/28	150 cc. physiologic solution of sodium chloride	9:05 a. m.	9:12 a. m.	9:45 a. m.	
	2/26/28	150 cc. peptonized milk	9:12 a. m.	9:17 a. m.	9:54 a. m.	
4	3/ 6/28	150 cc. physiologic solution of sodium chloride	9:15 a. m.	9:18 a. m.	10:00 a. m.	
	3/ 8/28	150 cc. indigo carmine	8:45 a. m.	8:53 a. m.	9:15 a. m.	At 10 a. m. indigo carmine appeared in urine
	3/ 9/28	Inflation of air into lower bowel	9:05 a. m.	None appeared as late as 1 hr. thereafter		
5	3/11/28	150 cc. physiologic solution of sodium chloride	8:45 a. m.	8:48 a. m.	9:20 a. m.	
6	3/13/28	150 cc. peptonized milk	9:00 a. m.	9:12 a. m.	10:00 a. m.	
7	3/26/28	150 cc. methylene blue	9:05 a. m.	9:17 a. m.	9:35 a. m.	At 10:30 a. m. methylene blue made its appearance in urine
8	4/ 2/28	150 Gm. dextrose.....	9:20 a. m.	9:27 a. m.	10:15 a. m.	Blood sugar determination: 9:10 a. m., 180 mg. 10:10 a. m., 192 mg. 12:15 p. m., 200 mg.

whether the mechanism was one of secretion or expulsion. To do this we employed the dye method of visualization of the gallbladder. The sodium salt of tetraiodophenolphthalein was given to the patient in capsule form at the time of passing the duodenal tube (i.e., the night before), and x-ray plates were made the next day at twelve and sixteen hour intervals after ingestion of the dye. Directly after the sixteen hour plates were taken, one of the various aforementioned solutions was instilled into the rectum and the time of flow of bile and its duration were

recorded. One hour after the rectal instillation, when the flow of bile had already ceased (which was seventeen hours after the administration of the dye capsules), another plate of the gallbladder was taken, and this was repeated at the eighteenth hour. At the nineteenth hour the usual fatty meal was given, and at the twentieth and thirty-sixth hours, plates were again made of the region of the gallbladder.

GROUP 2: CASE 1.—F. X, a man, aged 65, was admitted to the hospital for observation of the condition of the gallbladder.

On the evening of March 13, 1928, the patient was given a cleansing enema, and then tetraiodophenolphthalein in capsules was administered by the oral method. The duodenal tube was passed. The following morning, at the end of the twelve hour period, x-ray plates revealed the gallbladder fairly well filled out with the dye. At the sixteenth hour the x-ray picture showed the shadow to be practically of the same size but markedly increased in intensity.

The patient was then given 150 cc. of physiologic solution of sodium chloride per rectum, and within ten minutes a flow of bile was obtained from the duodenal tube. This steady drainage continued for thirty-five minutes. At the seventeenth, eighteenth and nineteenth hour periods, which corresponded to ten minutes and two hours after the rectal injection of the physiologic solution of sodium chloride, with its subsequent drainage of bile, the x-ray picture showed no reduction in the size of the gallbladder, but some intensification of the shadow. The duodenal tube was then removed, and the patient was given a fatty meal. Roentgen examination one hour after this food intake showed the gallbladder had emptied of the dye (fig.).

CASE 2.—P. D., a man, aged 66, was admitted to the hospital on account of varicose veins of the lower part of the left leg.

On the evening of March 23, 1928, the patient received the usual preparations, as in case 1. Twelve hours after the intake of the dye, no distinct shadow was visible. At the sixteenth hour, the shadow of the gallbladder could be fairly well outlined and appeared to be regular. The patient was then given a rectal injection of 150 cc. of peptonized milk, with the same result as regards the flow of bile from the duodenal tube as had been obtained in the previous cases.

Roentgen examinations were made one and two hours after the rectal injection. There was a marked concentration of the dye in the gallbladder, but no evidence of emptying. The patient was then given a meal and reexamined one hour later. The gallbladder was found markedly reduced in size. At the thirty-sixth hour, the shadow had entirely disappeared. Subsequent examination revealed no evidence of pathologic changes in the gallbladder.

CASE 3.—W. K., a boy, aged 15, was admitted to the hospital with a diagnosis of chronic nephritis.

On April 1, 1928, the procedure mentioned in the preceding two cases was repeated. X-ray plates of the gallbladder taken after the injection of the peptonized milk into the rectum showed no emptying of the gallbladder in spite of the fact that bile was obtained through the duodenal tube.

CASE 4.—L. C., a man, aged 28, was admitted to the hospital for observation.

On April 4, 1928, at the twelve hour period after the intake of the dye capsules, the gallbladder was not visible. At the sixteen-hour period, the shadow of the gallbladder was present. One hour after the injection of 150 cc. of peptonized milk into the rectum, the shadow of the gallbladder had not decreased in size

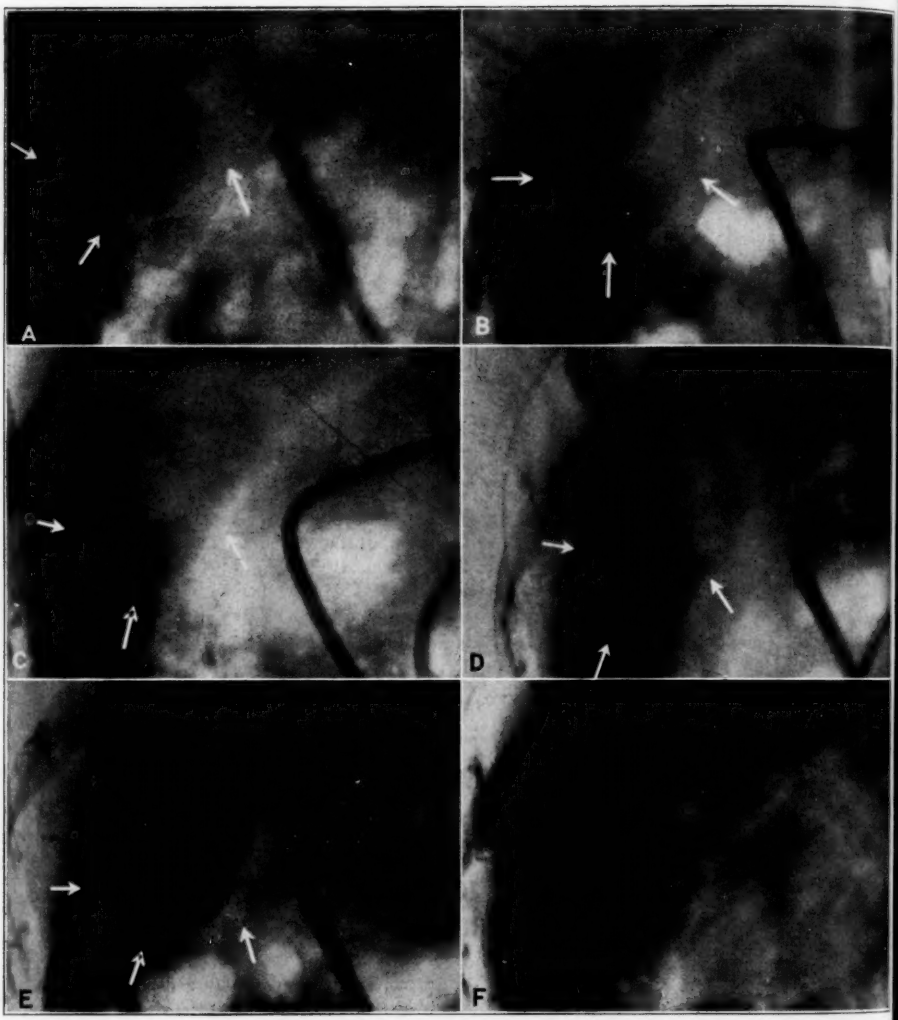

Fig. 1.—*A*, a roentgenogram, showing the dye method of visualization of the gallbladder, taken twelve hours after the administration of tetraiodophenolphthalein by capsules. *B* shows the extent of the shadow sixteen hours after the administration of capsules of tetraiodophenolphthalein; *C*, the extent of the shadow ten minutes after the administration of a physiologic solution of sodium chloride per rectum; *D*, the extent of the shadow eighteen hours after the administration of capsules of tetraiodophenolphthalein, and one hour after injection of a physiologic solution of sodium chloride by rectum; *E*, the extent of the shadow nineteen hours after the administration of the capsules and two hours after injection of a physiologic solution of sodium chloride by rectum, and *F*, the extent of the shadow twenty hours after the administration of capsules and one hour after eating.

but had become more intensified. At the two hour period after the injection, the shadow did not show up well because the patient breathed.

CASE 5.—E. W., a man, aged 24, was admitted to the hospital for observation but no pathologic process was found.

On April 15, 1928, twelve hours after the dye had been taken by mouth, a definite shadow of the gallbladder was seen. Sixteen hours later, the shadow of the gallbladder was slightly contracted. One hour later, 150 cc. of physiologic solution of sodium chloride was injected into the rectum, and shortly thereafter a flow of bile was obtained from the duodenal tube.

At the eighteenth hour, or one hour after injection of fluid into the rectum, the shadow of the gallbladder was more intensified and slightly larger in size. At the nineteenth hour, or two hours after the injection of physiologic solution of sodium chloride, the shadow of the gallbladder was still intense and remained about the same size. The patient was then given the fatty meal by mouth, and one hour after eating, which corresponded to the twenty-hour period after the intake of the dye capsules, the gallbladder appeared contracted and half the size. Thirty-six hours after the patient had taken the capsules no shadow of the gallbladder could be made out.[1]

COMMENT

In former years, irrigation of the colon was an established treatment for various types of jaundice. This paper offers the first proved experimental demonstration of the possible efficacy of this form of therapy.

In each of eight cases it was uniformly noted that within a period varying from three to twelve minutes after the instillation of various solutions high into the rectum, a flow of bile was obtained from the duodenal tube. This flow would continue for a period varying from eighteen to even as long as sixty-one minutes without any interruption. In three of the patients the rectal instillations were repeated once and in one of them twice. The solutions employed for instillation were, physiologic solution of sodium chloride, indigo carmine, peptonized milk, methylene blue, dextrose and phenolphthalein. This variety certainly precludes the possibility of any specificity in the response on the part of the liver. In one instance, case 4 (group 1) air was used to inflate the lower bowel, but no flow of bile was obtained as a result of this procedure, although the response had been obtained twice before in this patient after the use of physiologic solution of sodium chloride and a solution of indigo carmine. This fact would speak against a mechanical or nervous stimulation resulting from the mere filling of the rectum as being a cause for the secretion of bile. In the cases in which indigo carmine, methylene blue and phenolphthalein were employed, it was proved that these solutions were actually absorbed from the lower bowel, as they were detected in the urine at varying intervals after the rectal instillations. Similarly, in case 8 (group 1) a diabetic patient on whom dextrose solution was

1. Only the x-ray plates in connection with case 1 are reproduced. The x-ray pictures in association with the other cases are just as striking, but were not published on account of lack of space.

employed, the blood sugar determinations showed a progressive rise at the one and three hour periods.

These facts thus reveal that the introduction of various solutions into the lower bowel causes a definite flow of bile into the intestines. The mechanism whereby this is brought about is either a direct stimulation of the cells of the liver from the absorption of the instilled fluids into the portal system or a reflex nervous phenomenon. The former is the more probable explanation.

Further study will be undertaken to prove this point by the use of agents which are known to have a direct stimulating effect on the liver cells and by noting the quantity of bile obtained in comparison with the agents which are not especially cholagogue in action. This method of bile drainage may prove of therapeutic importance in those cases in which bile drainage by means of Lyon's method is impossible or inadvisable.

Another group of cases was studied for the purpose of determining whether such flow of bile was the result of stimulation of the bile-secreting or bile-expelling organs. Conclusive proof is offered by means of the x-ray picture (fig.). Twelve hours after the ingestion of the tetraiodophenolphthalein, a fairly large and distinct shadow of the gallbladder is present. At the sixteen-hour period the shadow is slightly larger and more intense. At the seventeenth hour, the physiologic solution of sodium chloride is introduced rectally, and ten minutes later, when the bile commences to flow, another plate taken shows the gallbladder about the same size as that previously noted but slightly more intense. The physiologic solution of sodium chloride is given at approximately the time when the usual fatty meal is employed to stimulate the contractions of the gallbladder. After a profuse flow of bile is obtained, other plates, taken at the eighteenth hour or one hour after the introduction of the physiologic solution of sodium chloride per rectum, and at the nineteenth hour, or two hours following the rectal instillations, reveal the gallbladder to be practically the same size as at the sixteenth hour and the shadow slightly more intensified. On the other hand, the usual fatty meal then administered brings about contraction of the gallbladder so that at the twentieth hour the shadow of the gallbladder is practically absent.

CONCLUSION

The introduction of various solutions into the upper rectum produces a drainage of the bile into the duodenum. This flow comes directly from the liver without contraction of the gallbladder.

Book Reviews

MUSCLE FUNCTION. By WILHELMINE G. WRIGHT. Cloth. Price, $3.50. Pp. 188, with 26 illustrations. New York: Paul B. Hoeber.

Wright's "Muscle Function" fills a space long left vacant in orthopedic literature; that of a practical discourse on the function of muscles presented in a readily available form as an aid to the surgeon and the physical therapist. Here is a work at once practical and exact, grown out of the constant observation of a skilled physiotherapist at one of the best infantile paralysis clinics in the country. At this clinic the author was guided in her work by the late Dr. Robert W. Lovett, to whom the treatise is respectfully dedicated. The foreword is by I. Playfair McMurrich, who points out that the method utilized in determining the exact function of the individual muscles and groups is superior to the anatomic and electrical methods, since, as Miss Wright emphasizes, it tells us not "what a muscle may do but what a muscle does do." Miss Wright has applied the physiologic method to patients whose paralyses make the confusing group and influences of antagonistic action less of a problem. By the elimination of superficial muscles the interpretation of the action of the deep-seated ones is made less difficult.

The work is divided into seven chapters: (1) general principles of muscle action; (2 to 6) movements of the limbs, head, neck, spine and respiration, and (7) a list of muscles giving the action in which each takes part. The illustrations are chiefly diagrammatic with a few taken from instructive cases seen at Dr. Lovett's clinic. They are too few in number but are well chosen in general. The final chapter makes an excellent reference for those who require an accurate and practical knowledge of the action of individual muscles and groups. Miss Wright's efforts are well worth while and should find a grateful group of enthusiasts.

TUMORES PRIMITIVOS DE LA PLEURA. By JOSE W. TOBIAS. Buenos Aires: Libreria El Ateneo, 1928.

This is a scholarly monograph of 479 pages on primary tumors of the pleura. Most of it is taken up with a discussion of the so-called endotheliomas of the pleura. The term includes perhaps many tumors which have their origin in the underlying epithelial tissue of the lung, but the terminology is so confusing that it is just as well to group these tumors under one head as the clinical syndrome is rather clearcut.

The author has made intensive pathologic studies on several such cases, and it seems likely that they really are endotheliomas. These are reported in detail and are lavishly illustrated with both gross and microscopic preparations, many in color.

Every feature of the disease is clearly outlined, and the literature on the subject is reviewed thoroughly. Illustrative cases are often given. The difficulty in diagnosis is emphasized, and several chapters are devoted to the signs, symptoms and diagnosis. It is unfortunate that the roentgenologic evidences are not more carefully analyzed. The prognosis is of course hopeless and the treatment purely symptomatic.

The remainder of the work is devoted to a less detailed discussion of the rarer sarcoma, the benign growths, granulomas and cysts.

THE TREATMENT OF VARICOSE VEINS BY INTRAVENOUS INJECTIONS. By J. P. L. MCLATCHIE. Price, $1.60. New York: The Macmillan Company, 1929.

This is a small monograph of fifty pages. It consists mainly of detailed descriptions of the preparation of the solutions used for injections and of the technic of

injections. Sodium salicylate is recommended most highly and quinine is the next choice in cases in which the pain from the former is too great. Emphasis is placed on the fact that any obliterative or coagulant solution spilled in the tissues is liable to cause extensive sloughing.

While the work has value as a technical handbook, it does not even begin to answer the important question as to whether treatment by injection is the method of choice. The author assumes that it is, and states that there never has been an embolus from the injection of quinine, a statement which is open to grave doubt. The whole matter of emboli, sloughing, whether real cures are brought about and whether either the morbidity or the mortality is less than in open operation cannot be considered as settled until a detailed analysis of parallel series of cases is published showing the true facts of the case. Such a work is far more needed than the present publication.

AN INDEX OF SYMPTOMATOLOGY. Edited by H. LETHEBY TIDY. Price, $12. Pp. 710. New York: William Wood & Company, 1929.

The book is intended to provide an account of the symptomatology of diseases. A clear and reasonably full description of the clinical manifestations of each disease is included, as are the usual and most important complications. No method of treatment is given. The contributors are all English and are men of wide reputation. Each description is signed. The fields of medicine, surgery, gynecology and various special subjects have been well covered. This book should be of great value to any one looking for a concise description of diseases and not caring to enter the fields of physiology or pathology as applied to them. It is well edited, and the purpose for which the book was written is amply fulfilled.

MODERN MEDICINE: Its Theory and Practice in Original Contributions by American and Foreign Authors. Edited by Sir William Osler, Bart., M.D., F.R.S. Third edition, thoroughly revised, reedited by Thomas McCrae, M.D., assisted by Elmer H. Funk, M.D. General Index. Price, $1. Philadelphia: Lea & Febiger, 1928.

This is a volume of 126 pages containing a complete index of Osler and McCrae's "Modern Medicine." The index is exhaustive and accurate. Bound separately in a handy volume it serves an excellent purpose as to convenience. Through it, all the subject matter of the six bulky volumes of this great work is made readily available.

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